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(54) Titre : ANTIGENES DE STREPTOCOCCUS PYOGENES  
(54) Title: STREPTOCOCCUS PYOGENES ANTIGEN

(57) Abrégé/Abstract:

The present invention relates to an antigen of Streptococcus pyogenes (also called group A Streptococcus (GAS)), which is useful as vaccine component for therapy and/or prophylaxis.

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(54) Title: STREPTOCOCCUS PYOGENES ANTIGEN

(57) Abstract: The present invention relates to an antigen of *Streptococcus pyogenes* (also called group A *Streptococcus* (GAS)), which is useful as vaccine component for therapy and/or prophylaxis.

STREPTOCOCCUS PYOGENES ANTIGENS5 FIELD OF THE INVENTION

The present invention is related to antigens, more particularly a polypeptide antigen of Streptococcus pyogenes (also called group A Streptococcus (GAS)) bacterial pathogen which may be useful for prophylaxis, diagnostic and/or therapy of streptococcal infection.

BACKGROUND OF THE INVENTION

Streptococci are gram (+) bacteria which are differentiated by group specific carbohydrate antigens A through O which are found at the cell surface. Streptococcus pyogenes isolates are further distinguished by type-specific M protein antigens. M proteins are important virulence factors which are highly variable both in molecular weights and in sequences. Indeed, more than 80-M protein types have been identified on the basis of antigenic differences.

Streptococcus pyogenes is responsible for many diverse infection types, including pharyngitis, erysipelas and impetigo, scarlet fever, and invasive diseases such as bacteremia and necrotizing fasciitis and also toxic shock. A resurgence of invasive disease in recent years has been documented in many countries, including those in North America and Europe. Although the organism is sensitive to antibiotics, the high attack rate and rapid onset of sepsis results in high morbidity and mortality.

To develop a vaccine that will protect individuals from Streptococcus pyogenes infection, efforts have concentrated on virulence factors such as the type-specific M proteins. However, the amino-terminal portion of M proteins was found to induce cross-reactive antibodies which reacted with human myocardium, tropomyosin, myosin, and vimentin, which might be implicated in

autoimmune diseases. Others have used recombinant techniques to produce complex hybrid proteins containing amino-terminal peptides of M proteins from different serotypes. However, a safe vaccine containing all Streptococcus pyogenes serotypes will be highly complex to produce and standardize.

In addition to the serotype-specific antigens, other Streptococcus pyogenes proteins have generated interest as potential vaccine candidates. The C5a peptidase, which is expressed by at least Streptococcus pyogenes 40 serotypes, was shown to be immunogenic in mice, but its capacity to reduce the level of nasopharyngeal colonization was limited. Other investigators have also focused on the streptococcal pyrogenic exotoxins which appear to play an important role in pathogenesis of infection. Immunization with these proteins prevented the deadly symptoms of toxic shock, but did not prevent colonization.

Therefore there remains an unmet need for *Streptococcus pyogenes* antigens that may be used vaccine components for prophylaxis, diagnostic and/or therapy of Streptococcus infection.

#### SUMMARY OF THE INVENTION

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20 or fragments, analogues or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 95% identity to a second polypeptide comprising a sequence chosen from SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20 or fragments, analogues or derivatives thereof.

In other aspects, there are provided novel polypeptides encoded

by polynucleotides of the invention, vectors comprising polynucleotides of the invention operably linked to an expression control region, as well as host cells transfected with said vectors, pharmaceutical or vaccine compositions and  
5 methods of producing polypeptides comprising culturing said host cells under conditions suitable for expression.

#### BRIEF DESCRIPTION OF THE DRAWINGS

10

Figure 1 is the DNA sequence of BVH-P1 gene from serotype 3 S. pyogenes strain ATCC12384 with a secretion signal at position 1 to 75; SEQ ID NO:1.

15 Figure 2 is the amino acid sequence BVH-P1 protein from serotype 3 S. pyogenes strain ATCC12384 with a secretion signal at position 1 to 25; SEQ ID NO:2.

Figure 3 is the DNA sequence of BVH-P1 gene from S. pyogenes  
20 strain LSPQ2699(ATCC19615) with a secretion signal at position 1 to 75; SEQ ID NO:3.

Figure 4 is the amino acid sequence BVH-P1 protein from S. pyogenes  
strain LSPQ2699(ATCC19615) with a secretion signal at position 1 to  
25 25; SEQ ID NO:4.

Figure 5 is the DNA sequence of BVH-P1 gene from S. pyogenes strain SPY57 with a secretion signal at position 1 to 75; SEQ ID NO:5.

30

Figure 6 is the amino acid sequence BVH-P1 protein from S. pyogenes strain SPY57 with a secretion signal at position 1 to 25; SEQ ID NO:6.

Figure 7 is the DNA sequence of BVH-P1 gene from S. pyogenes strain B514 with a secretion signal at position 1 to 75; SEQ ID NO:7.

- 5 Figure 8 is the amino acid sequence BVH-P1 protein from S. pyogenes strain B514 with a secretion signal at position 1 to 25; SEQ ID NO:8.

- 10 Figure 9 is the DNA sequence BVH-P1 gene without a secretion signal from serotype 3 S.pyogenes strain ATCC12384 ; SEQ ID NO:9.

- 15 Figure 10 is the amino acid sequence BVH-P1 protein without a secretion signal from serotype 3 S.pyogenes strain ATCC12384 ; SEQ ID NO:10.

- 20 Figure 11 is the DNA sequence BVH-P1 gene without a secretion signal from serotype 3 S.pyogenes strain LSPQ2699 (ATCC19615) ; SEQ ID NO:11.

- Figure 12 is the amino acid sequence BVH-P1 protein without a secretion signal from serotype 3 S.pyogenes strain LSPQ2699 (ATCC19615) ; SEQ ID NO:12.

- 25 Figure 13 is the DNA sequence BVH-P1 gene without a secretion signal from serotype 3 S.pyogenes strain SPY57 ; SEQ ID NO:13.

- 30 Figure 14 is the amino acid sequence BVH-P1 protein without a secretion signal from serotype 3 S.pyogenes strain SPY57 ; SEQ ID NO:14.

Figure 15 is the DNA sequence BVH-P1 gene without a secretion signal from serotype 3 S.pyogenes strain B514 ; SEQ ID NO:15.

Figure 16 is the amino acid sequence BVH-P1 protein without a secretion signal from serotype 3 S.pyogenes strain B514 ; SEQ ID NO:16.

5 Figure 17 depicts the comparison of the nucleotide sequences of the BVH-P1 genes from ATCC12384, LSPQ2699(ATCC19615), SPY57, B514, ATCC 70029 (Oklahoma) and T28/51/4 (U09352) S. pyogenes strains by using the program Clustal W from MacVector sequence analysis software (version 6.5). Underneath the alignment, there  
10 is a consensus line. Shaded nucleotides are identical between every sequences and gaps in the sequence introduced by alignment are indicated by hyphens.

Figure 18 depicts the comparison of the predicted amino acid  
15 sequences of the BVH-P1 open reading frames from ATCC12384, LSPQ2699(ATCC19615), SPY57, B514, ATCC 70029 (Oklahoma) and T28/51/4 (U09352) S. pyogenes strains by using the program Clustal W from MacVector sequence analysis software (version 6.5). Underneath the alignment, there is a consensus  
20 line. Shaded amino acid residues are identical between every sequences and gaps in the sequence introduced by alignment are indicated by hyphens.

Figure 19 is the DNA sequence of a gene from S. pneumonia; SEQ  
25 ID NO:17.

Figure 20 is the amino acid sequence of a protein from S. pneumonia; SEQ ID NO:18.

30

#### DETAILED DESCRIPTION OF THE INVENTION

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide comprising a sequence  
35 chosen from SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20 or fragments, analogues or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide having at least 95% identity to a second polypeptide comprising a sequence  
5 chosen from SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20 or fragments, analogues or derivatives thereof.

According to one aspect, the present invention relates to polypeptides characterized by the amino acid sequence comprising  
10 SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20 or fragments, analogues or derivatives thereof.

According to one aspect, the present invention provides an isolated polynucleotide encoding a polypeptide capable of  
15 generating antibodies having binding specificity for a polypeptide comprising a sequence chosen from SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20 or fragments, analogues or derivatives thereof.

20 In accordance with the present invention, there is provided a consensus nucleotide sequence depicted in Figure 17. As can be seen by the alignment, the polynucleotide encoding the polypeptide of the invention is well conserved. Without restricting the scope of the invention, the following table 1  
25 shows the possible modifications. SEQ ID NO:19 covers the consensus nucleotide sequence depicted in Figure 17 with the modifications illustrated in Table 1:

Position on alignment in Figure 17	Possible nucleotide
21	C or T
53	C or T
69	G or A
103	G or C
149	C or T



150	A or T
195	G or A
244	T or C
273	A or C
282	T or C
302	C or A
318	A or G
334	G or T
394	C or T
400	G or A
415	C or T
428-448	[CTGATGTCCCAACGACACCAT] or none
450	C or A
473	C or T
501	G or A
527	T or C
572	T or A
573	T or A
595	A or C
596	C or G
597	G or C
630	A or G
632	A or C
633	C or T
634	C or T
665	A or G
666	G or A
683	T or C
708	C or T
733	[CAGATGTAACT] or none
798	T or C
883	G or none
927	T or A

930	T or C
943	T or none
952	T or A
955	G or A
964	T or C
973	G or A
976	T or G
978	A or T
979	A or T
981	A or G
982	T or C
986	G or A
988	T or G
1033	G or C
1034	C or G
1102	C or T
1143	A or T
1144	A or T
1145	A or T
1146	A or T

In accordance with the present invention, there is provided a consensus amino acid sequence depicted in Figure 18. As can be seen by the alignment, the polypeptide of the invention is well conserved. Without restricting the scope of the invention, the following table 2 shows the possible modifications. SEQ ID NO:20 covers the consensus nucleotide sequence depicted in Figure 18 with the modifications illustrated in Table 2:

Position on alignment in Figure 18	Possible amino acid
18	A or V
35	E or Q
50	T or I
101	T or N
112	A or S
132	P or S
134	V or I
139	S or P
143 to 149	SDVPTTP or none
150	F or L
158	S or F
176	L or s
191	V or E
199	T or P or S
211	D or A
212	P or S
222	E or G
228	V or A
242 to 245	ETSQ or none
246	E or M
247	T or L
248	S or T
295	A or L
296	S or L
297	A or P
298	F or L
299	G or V
300	I or L
301	T or R
302	S or H
303	F or L

304	S or V
305	G or V
306	Y or T
307	R or V
308	P or Q
309	G or E
310	D or I
311	P or Q
312	G or E
313	D or I
314	H or I
326	E or V
327	N or S
329	A or T
344	E or D
345	R or G
380	E or V
381	N or F

In accordance with the present invention, all polynucleotides encoding polypeptides are within the scope of the present  
5 invention.

In a further embodiment, the polypeptides in accordance with the present invention are antigenic.

10 In a further embodiment, the polypeptides in accordance with the present invention are immunogenic.

In a further embodiment, the polypeptides in accordance with the present invention can elicit an immune response in an  
15 individual.

In a further embodiment, the present invention also relates to

polypeptides which are able to raise antibodies having binding specificity to the polypeptides of the present invention as defined above.

- 5 An antibody that "has binding specificity" is an antibody that recognizes and binds the selected polypeptide but which does not substantially recognize and bind other molecules in a sample, e.g., a biological sample. Specific binding can be measured using an ELISA assay in which the selected polypeptide is used  
10 as an antigen.

In accordance with the present invention, "protection" in the biological studies is defined by a significant increase in the survival curve, rate or period. Statistical analysis using the  
15 Log rank test to compare survival curves, and Fisher exact test to compare survival rates and numbers of days to death, respectively, might be useful to calculate P values and determine whether the difference between the two groups is statistically significant. P values of 0.05 are regarded as not  
20 significant.

As used herein, "fragments", "analogues" or "derivatives" of the polypeptides of the invention include those polypeptides in which one or more of the amino acid residues are substituted  
25 with a conserved or non-conserved amino acid residue (preferably conserved) and which may be natural or unnatural. In one embodiment, derivatives and analogues of polypeptides of the invention will have about 70% identity with those sequences illustrated in the figures or fragments thereof. That is, 70%  
30 of the residues are the same. In a further embodiment, polypeptides will have greater than 75% homology. In a further embodiment, polypeptides will have greater than 80% homology. In a further embodiment, polypeptides will have greater than 85% homology. In a further embodiment, polypeptides will have  
35 greater than 90% homology. In a further embodiment, polypeptides will have greater than 95% homology. In a further embodiment,

- polypeptides will have greater than 99% homology. In a further embodiment, derivatives and analogues of polypeptides of the invention will have less than about 20 amino acid residue substitutions, modifications or deletions and more preferably less than 10. Preferred substitutions are those known in the art as conserved i.e. the substituted residues share physical or chemical properties such as hydrophobicity, size, charge or functional groups.
- 10 The skilled person will appreciate that fragments, analogues or derivatives of the proteins or polypeptides of the invention will also find use in the context of the present invention, i.e. as antigenic/immunogenic material. Thus, for instance proteins or polypeptides which include one or more additions, deletions, 15 substitutions or the like are encompassed by the present invention. In addition, it may be possible to replace one amino acid with another of similar "type". For instance replacing one hydrophobic amino acid with another hydrophobic amino acid.
- 20 One can use a program such as the CLUSTAL program to compare amino acid sequences. This program compares amino acid sequences and finds the optimal alignment by inserting spaces in either sequence as appropriate. It is possible to calculate amino acid identity or similarity (identity plus conservation of 25 amino acid type) for an optimal alignment. A program like BLASTx will align the longest stretch of similar sequences and assign a value to the fit. It is thus possible to obtain a comparison where several regions of similarity are found, each having a different score. Both types of identity analysis are 30 contemplated in the present invention.

In an alternative approach, the analogues or derivatives could be fusion proteins, incorporating moieties which render purification easier, for example by effectively tagging the 35 desired protein or polypeptide, it may be necessary to remove

the "tag" or it may be the case that the fusion protein itself retains sufficient antigenicity to be useful.

In an additional aspect of the invention there are provided  
5 antigenic/immunogenic fragments of the proteins or polypeptides of the invention, or of analogues or derivatives thereof.

The fragments of the present invention should include one or more epitopic regions or be sufficiently similar to such regions  
10 to retain their antigenic/immunogenic properties. Thus, for fragments according to the present invention the degree of identity is perhaps irrelevant, since they may be 100% identical to a particular part of a protein or polypeptide, homologue or derivative as described herein. The key issue, once again, is  
15 that the fragment retains the antigenic/immunogenic properties.

Thus, what is important for analogues, derivatives and fragments is that they possess at least a degree of the antigenicity/immunogenic of the protein or polypeptide from  
20 which they are derived.

Also included are polypeptides which have fused thereto other  
compounds which alter the polypeptides biological or pharmacological properties i.e. polyethylene glycol (PEG) to  
25 increase half-life; leader or secretory amino acid sequences for ease of purification; prepro- and pro- sequences; and (poly)saccharides.

Furthermore, in those situations where amino acid regions are  
30 found to be polymorphic, it may be desirable to vary one or more particular amino acids to more effectively mimic the different epitopes of the different streptococcus strains.

Moreover, the polypeptides of the present invention can be  
35 modified by terminal  $-NH_2$  acylation (eg. by acetylation, or

thioglycolic acid amidation, terminal carbosy amidation, e.g. with ammonia or methylamine) to provide stability, increased hydrophobicity for linking or binding to a support or other molecule.

5

Also contemplated are hetero and homo polypeptide multimers of the polypeptide fragments, analogues and derivatives. These polymeric forms include, for example, one or more polypeptides that have been cross-linked with cross-linkers such as  
10 avidin/biotin, gluteraldehyde or dimethylsuperimide. Such polymeric forms also include polypeptides containing two or more tandem or inverted contiguous sequences, produced from multicistronic mRNAs generated by recombinant DNA technology.

15 Preferably, a fragment, analog or derivative of a polypeptide of the invention will comprise at least one antigenic region i.e. at least one epitope.

In order to achieve the formation of antigenic polymers (i.e. synthetic multimers), polypeptides may be utilized having  
20 bishaloacetyl groups, nitroarylhalides, or the like, where the reagents being specific for thio groups. Therefore, the link between two mercapto groups of the different peptides may be a single bond or may be composed of a linking group of at least  
25 two, typically at least four, and not more than 16, but usually not more than about 14 carbon atoms.

In a particular embodiment, polypeptide fragments, analogues and derivatives of the invention do not contain a methionine (Met)  
30 starting residue. Preferably, polypeptides will not incorporate a leader or secretory sequence (signal sequence). The signal portion of a polypeptide of the invention may be determined according to established molecular biological techniques. In general, the polypeptide of interest may be isolated from a  
35 streptococcal culture and subsequently sequenced to determine the initial residue of the mature protein and therefore the



sequence of the mature polypeptide.

According to another aspect, there are provided vaccine compositions comprising one or more streptococcal polypeptides  
5 of the invention in admixture with a pharmaceutically acceptable carrier diluent or adjuvant. Suitable adjuvants include oils i.e. Freund's complete or incomplete adjuvant; salts i.e.  $\text{AlK}(\text{SO}_4)_2$ ,  $\text{AlNa}(\text{SO}_4)_2$ ,  $\text{AlNH}_4(\text{SO}_4)_2$ , silica, kaolin, carbon polynucleotides i.e. poly IC and poly AU. Preferred adjuvants  
10 include QuilA and Alhydrogel. Vaccines of the invention may be administered parenterally by injection, rapid infusion, nasopharyngeal absorption, dermoabsorption, or bucal or oral. Pharmaceutically acceptable carriers also include tetanus toxoid.

15

The term vaccine is also meant to include antibodies. In accordance with the present invention, there is also provided the use of one or more antibodies having binding specificity for the polypeptides of the present invention for the treatment or  
20 prophylaxis of streptococcus infection and/or diseases and symptoms mediated by streptococcus infection.

Vaccine compositions of the invention are used for the treatment or prophylaxis of streptococcal infection and/or diseases and  
25 symptoms mediated by streptococcal infection As described in P.R. Murray (Ed, in chief), E.J. Baron, M.A. Pfaller, F.C. Tenover and R.H. Tenover. Manual of Clinical Microbiology, ASM Press, Washington, D.C. sixth edition, 1995, 1482p which are herein incorporated by reference. In one embodiment, vaccine  
30 compositions of the present invention are used for the prophylaxis or treatment of pharyngitis, erysipelas and impetigo, scarlet fever, and invasive diseases such as bacteremia and necrotizing fasciitis and also toxic shock. In one embodiment, vaccine compositions of the invention are used  
35 for the prophylaxis or treatment of streptococcus infection and/or diseases and symptoms mediated by streptococcus

infection, in particular group A *streptococcus* (*pyogenes*), group B *streptococcus* (GBS or *agalactiae*), *S.pneumoniae*, *dysgalactiae*, *uberis*, *nocardia* as well as *Staphylococcus aureus*. In a further embodiment, the streptococcus infection is Streptococcus  
5 pyogenes.

In a particular embodiment, vaccines are administered to those individuals at risk of streptococcus infection such as infants, elderly and immunocompromised individuals.

10

As used in the present application, the term " individuals" include mammals. In a further embodiment, the mammal is human.

Vaccine compositions are preferably in unit dosage form of about  
15 0.001 to 100 µg/kg (antigen/body weight) and more preferably 0.01 to 10 µg/kg and most preferably 0.1 to 1 µg/kg 1 to 3 times with an interval of about 1 to 6 week intervals between immunizations.

20 Vaccine compositions are preferably in unit dosage form of about 0.1 µg to 10 mg and more preferably 1µg to 1 mg and most preferably 10 to 100 µg 1 to 3 times with an interval of about 1 to 6 week intervals between immunizations.

25 According to another aspect, there are provided polynucleotides encoding polypeptides characterized by the amino acid sequence chosen from SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20 or fragments, analogues or derivatives thereof.

30 In one embodiment, polynucleotides are those illustrated in SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 19 which may include the open reading frames (ORF), encoding polypeptides of the invention.

It will be appreciated that the polynucleotide sequences  
35 illustrated in the figures may be altered with degenerate codons

yet still encode the polypeptides of the invention. Accordingly the present invention further provides polynucleotides which hybridize to the polynucleotide sequences herein above described (or the complement sequences thereof) having 50% identity  
5 between sequences. In one embodiment, at least 70% identity between sequences. In one embodiment, at least 75% identity between sequences. In one embodiment, at least 80% identity between sequences. In one embodiment, at least 85% identity between sequences. In one embodiment, at least 90% identity  
10 between sequences. In a further embodiment, polynucleotides are hybridizable under stringent conditions i.e. having at least 95% identity. In a further embodiment, more than 97% identity.

Suitable stringent conditions for hybridation can be readily  
15 determined by one of skilled in the art (see for example Sambrook et al., (1989) Molecular cloning : A Laboratory Manual, 2<sup>nd</sup> ed, Cold Spring Harbor, N.Y.; Current Protocols in Molecular Biology, (1999) Edited by Ausubel F.M. et al., John Wiley & Sons, Inc., N.Y.).

20

In a further embodiment, the present invention provides polynucleotides that hybridise under stringent conditions to either

- (a) a DNA sequence encoding a polypeptide or
  - 25 (b) the complement of a DNA sequence encoding a polypeptide;
- wherein said polypeptide comprising a sequence chosen from SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20 or fragments or analogues thereof.

- 30 In a further embodiment, the present invention provides polynucleotides that hybridise under stringent conditions to either
- (a) a DNA sequence encoding a polypeptide or
  - (b) the complement of a DNA sequence encoding a polypeptide;
- 35 wherein said polypeptide comprises at least 10 contiguous amino acid residues from a polypeptide comprising a sequence chosen from

SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 20 or fragments or analogues thereof.

In a further embodiment, polynucleotides are those encoding polypeptides of the invention illustrated in SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 20.

In a further embodiment, polynucleotides are those illustrated in SEQ ID NOS : 1, 3, 5, 7, 9, 11, 13, 15, 19 encoding polypeptides of the invention.

As will be readily appreciated by one skilled in the art, polynucleotides include both DNA and RNA.

The present invention also includes polynucleotides complementary to the polynucleotides described in the present application.

In a further aspect, polynucleotides encoding polypeptides of the invention, or fragments, analogues or derivatives thereof, may be used in a DNA immunization method. That is, they can be incorporated into a vector which is replicable and expressible upon injection thereby producing the antigenic polypeptide in vivo. For example polynucleotides may be incorporated into a plasmid vector under the control of the CMV promoter which is functional in eukaryotic cells. Preferably the vector is injected intramuscularly.

According to another aspect, there is provided a process for producing polypeptides of the invention by recombinant techniques by expressing a polynucleotide encoding said polypeptide in a host cell and recovering the expressed polypeptide product. Alternatively, the polypeptides can be produced according to established synthetic chemical techniques i.e. solution phase or solid phase synthesis of oligopeptides which are ligated to produce the full polypeptide (block

ligation).

General methods for obtention and evaluation of polynucleotides and polypeptides are described in the following references:

- 5 Sambrook et al, Molecular Cloning: A Laboratory Manual, 2nd ed, Cold Spring Harbor, N.Y., 1989; Current Protocols in Molecular Biology, Edited by Ausubel F.M. et al., John Wiley and Sons, Inc. New York; PCR Cloning Protocols, from Molecular Cloning to Genetic Engineering, Edited by White B.A., Humana Press, Totowa,  
10 New Jersey, 1997, 490 pages; Protein Purification, Principles and Practices, Scopes R.K., Springer-Verlag, New York, 3rd Edition, 1993, 380 pages; Current Protocols in Immunology, Edited by Coligan J.E. et al., John Wiley & Sons Inc., New York which are herein incorporated by reference.

15

- For recombinant production, host cells are transfected with vectors which encode the polypeptide, and then cultured in a nutrient media modified as appropriate for activating promoters, selecting transformants or amplifying the genes. Suitable  
20 vectors are those that are viable and replicable in the chosen host and include chromosomal, non-chromosomal and synthetic DNA sequences e.g. bacterial plasmids, phage DNA, baculovirus, yeast plasmids, vectors derived from combinations of plasmids and phage DNA. The polypeptide sequence may be incorporated in the  
25 vector at the appropriate site using restriction enzymes such that it is operably linked to an expression control region comprising a promoter, ribosome binding site (consensus region or Shine-Dalgarno sequence), and optionally an operator (control element). One can select individual components of the  
30 expression control region that are appropriate for a given host and vector according to established molecular biology principles (Sambrook et al, Molecular Cloning: A Laboratory Manual, 2nd ed, Cold Spring Harbor, N.Y., 1989; Current Protocols in Molecular Biology, Edited by Ausubel F.M. et al., John Wiley and Sons, Inc. New York incorporated herein by reference). Suitable  
35 promoters include but are not limited to LTR or SV40 promoter,

E.coli lac, tac or trp promoters and the phage lambda P<sub>L</sub> promoter. Vectors will preferably incorporate an origin of replication as well as selection markers i.e. ampicillin resistance gene. Suitable bacterial vectors include pET, pQE70, 5 pQE60, pQE-9, pbs, pD10 phagescript, psiX174, pbluescript SK, pbsks, pNH8A, pNH16a, pNH18A, pNH46A, ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 and eukaryotic vectors pBlueBacIII, pWLNEO, pSV2CAT, pOG44, pXT1, pSG, pSVK3, pBPV, pMSG and pSVL. Host cells may be bacterial i.e. E.coli, Bacillus subtilis, 10 Streptomyces; fungal i.e. Aspergillus niger, Aspergillus nidulins; yeast i.e. Saccharomyces or eukaryotic i.e. CHO, COS.

Upon expression of the polypeptide in culture, cells are typically harvested by centrifugation then disrupted by physical 15 or chemical means (if the expressed polypeptide is not secreted into the media) and the resulting crude extract retained to isolate the polypeptide of interest. Purification of the polypeptide from culture media or lysate may be achieved by established techniques depending on the properties of the 20 polypeptide i.e. using ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, hydroxylapatite chromatography and lectin chromatography. Final purification may be achieved using 25 HPLC.

The polypeptide may be expressed with or without a leader or secretion sequence. In the former case the leader may be removed using post-translational processing (see US 4,431,739; 30 US 4,425,437; and US 4,338,397 incorporated herein by reference) or be chemically removed subsequent to purifying the expressed polypeptide.

According to a further aspect, the streptococcal polypeptides of 35 the invention may be used in a diagnostic test for streptococcus infection, in particular Streptococcus pyogenes infection.

Several diagnostic methods are possible, for example detecting streptococcus organism in a biological sample, the following procedure may be followed:

- a) obtaining a biological sample from an individual;
- 5 b) incubating an antibody or fragment thereof reactive with a streptococcus polypeptide of the invention with the biological sample to form a mixture; and
- c) detecting specifically bound antibody or bound fragment in the mixture which indicates the presence of streptococcus.

10

Alternatively, a method for the detection of antibody specific to a streptococcus antigen in a biological sample containing or suspected of containing said antibody may be performed as follows:

- 15 a) obtaining a biological sample from an individual;
- b) incubating one or more streptococcus polypeptides of the invention or fragments thereof with the biological sample to form a mixture; and
- c) detecting specifically bound antigen or bound fragment in  
20 the mixture which indicates the presence of antibody specific to streptococcus.

One of skill in the art will recognize that this diagnostic test may take several forms, including an immunological test such as  
25 an enzyme-linked immunosorbent assay (ELISA), a radioimmunoassay or a latex agglutination assay, essentially to determine whether antibodies specific for the protein are present in an individual.

- 30 The DNA sequences encoding polypeptides of the invention may also be used to design DNA probes for use in detecting the presence of streptococcus in a biological sample suspected of containing such bacteria. The detection method of this invention comprises:

- 35 a) obtaining the biological sample from an individual;
- b) incubating one or more DNA probes having a DNA sequence

encoding a polypeptide of the invention or fragments thereof with the biological sample to form a mixture; and  
c) detecting specifically bound DNA probe in the mixture which indicates the presence of streptococcus bacteria.

5

The DNA probes of this invention may also be used for detecting circulating streptococcus i.e. Streptococcus pyogenes nucleic acids in a sample, for example using a polymerase chain reaction, as a method of diagnosing streptococcus infections.

10 The probe may be synthesized using conventional techniques and may be immobilized on a solid phase, or may be labelled with a detectable label. A preferred DNA probe for this application is an oligomer having a sequence complementary to at least about 6 contiguous nucleotides of the Streptococcus pyogenes  
15 polypeptides of the invention.

Another diagnostic method for the detection of streptococcus in an individual comprises:

- a) labelling an antibody reactive with a polypeptide of the invention or fragment thereof with a detectable label;  
20 b) administering the labelled antibody or labelled fragment to the patient; and  
c) detecting specifically bound labelled antibody or labelled fragment in the patient which indicates the presence of  
25 streptococcus.

A further aspect of the invention is the use of the streptococcus polypeptides of the invention as immunogens for the production of specific antibodies for the diagnosis and in  
30 particular the treatment of streptococcus infection. Suitable antibodies may be determined using appropriate screening methods, for example by measuring the ability of a particular antibody to passively protect against streptococcus infection in a test model. One example of an animal model is the mouse model  
35 described in the examples herein. The antibody may be a whole antibody or an antigen-binding fragment thereof and may belong



to any immunoglobulin class. The antibody or fragment may be of animal origin, specifically of mammalian origin and more specifically of murine, rat or human origin. It may be a natural antibody or a fragment thereof, or if desired, a recombinant antibody or antibody fragment. The term recombinant antibody or antibody fragment means antibody or antibody fragment which was produced using molecular biology techniques. The antibody or antibody fragments may be polyclonal, or preferably monoclonal. It may be specific for a number of epitopes associated with the Streptococcus pyogenes polypeptides but is preferably specific for one.

A further aspect of the invention is the use of the antibodies directed to the streptococcus polypeptides of the invention for passive immunization. One could use the antibodies described in the present application. Suitable antibodies may be determined using appropriate screening methods, for example by measuring the ability of a particular antibody to passively protect against streptococcus infection in a test model. One example of an animal model is the mouse model described in the examples herein. The antibody may be a whole antibody or an antigen-binding fragment thereof and may belong to any immunoglobulin class. The antibody or fragment may be of animal origin, specifically of mammalian origin and more specifically of murine, rat or human origin. It may be a natural antibody or a fragment thereof, or if desired, a recombinant antibody or antibody fragment. The term recombinant antibody or antibody fragment means antibody or antibody fragment which was produced using molecular biology techniques. The antibody or antibody fragments may be polyclonal, or preferably monoclonal. It may be specific for a number of epitopes associated with the streptococcus pneumoniae polypeptides but is preferably specific for one.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one

of ordinary skill in the art to which this invention belongs. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

10

## EXAMPLE 1

This example illustrates the cloning of S. pyogenes gene.

The coding region of S. pyogenes gene BVH-P1 (SEQ ID NO:1) was amplified by PCR (DNA Thermal Cycler GeneAmp PCR system 2400 Perkin Elmer, San Jose, CA) from genomic DNA of serotype 3 S. pyogenes strain ATCC12384 using the following oligos that contained base extensions for the addition of restriction sites NcoI (CCATGG) and XhoI (CTCGAG): DMAR16 (5'-CAGGCCATGGAGTGGACACCACGATCGGTTAC-3'); DMAR17 (5'-GCCGCTCGAGAGCATTAAAGGAGACATGAACATGATC-3'). PCR products were purified from agarose gel using a QIAquick gel extraction kit from QIAGEN following the manufacturer's instructions (Chatsworth, CA), and digested with NcoI and XhoI (Pharmacia Canada Inc, Baie d'Urfé, Canada). The pET-21d(+) vector (Novagen, Madison, WI) was digested with NcoI and XhoI and purified from agarose gel using a QIAquick gel extraction kit from QIAGEN (Chatsworth, CA). The NcoI-XhoI PCR products were ligated to the NcoI-XhoI pET-21d(+) expression vector. The ligated products were transformed into E. coli strain E. coli strain DH5 $\alpha$  [ $\phi$ 80dlacZAM15  $\Delta$ (lacZYA-argF)U169 endA1 recA1 hsdR17(r<sub>K</sub>-m<sub>K</sub>+) deoR thi-1 supE44  $\lambda$ gyrA96 relA1] (Gibco BRL, Gaithersburg, MD) according to the method of Simanis (Hanahan, D. DNA Cloning, 1985, D.M. Glover (ed), pp. 109-135). Recombinant pET-21d(+) plasmid (rpET21d(+)) containing BVH-P1

gene was purified using a QIAGEN plasmid kit (Chatsworth, CA) and DNA insert was sequenced (Tag Dye Deoxy Terminator Cycle Sequencing kit, ABI, Foster City, CA).

5 It was determined that the open reading frame (ORF) which codes for BVH-P1 contains 1170-bp and encodes a 389 amino acid residues polypeptide with a predicted pI of 4.37 and a predicted molecular mass of 41054 Da.

Analysis of the predicted amino acid residues sequence (SEQ ID  
10 NO:2) using the Spscan software (Wisconsin Sequence Analysis Package; Genetics Computer Group) suggested the existence of a  
25 amino acid residues signal peptide (MIITKKSLEFVTSVALSLAPLATAQA), which ends with a cleavage site situated between an alanine and a glutamine residues. Analysis  
15 of this ORF did not reveal the presence of repetitive structures, cell wall anchoring motif (LPXTG), or IgA binding motif (MLKKIE).

An ORF which shares 62% with the S. pyogenes BVH-P1 gene was  
20 initially presented in the patent application PCT/CA99/00114 which described Group B streptococcus antigens. BVH-P1 gene was also found to share homology (62% identity) with an ORF present in the genome of S. pneumoniae (The Institute for Genomic Research).

25

#### EXAMPLE 2

This example describes the PCR amplification and sequencing of BVH-P1 gene from other S. pyogenes strains and the evaluation of the level of molecular conservation of this gene.

30

Lancefield's serogroup A S. pyogenes LSPQ2296 (ATCC 19615) was provided by the laboratoire de la santé publique du Québec, Sainte-Anne-de-Bellevue; serotype 1 S. pyogenes SPY57 clinical isolate was provided by the centre de recherche en infectiologie  
35 du centre hospitalier de l'université Laval, Sainte-Foy; and S. pyogenes strain B514 which was initially isolated from a mouse

was provided by Susan Hollingshead, from University of Alabama, Birmingham. The respective coding region of S. pyogenes gene BVH-P1 from strains ATCC 12384 (SEQ ID NO:1), LSPQ2699(ATCC19615) (SEQ ID NO:3), SPY57 (SEQ ID NO:5), and B514 (SEQ ID NO:7) were amplified by PCR (DNA Thermal Cycler GeneAmp PCR system 2400 Perkin Elmer, San Jose, CA) from bacterial cell lysates using the following oligos DMAR69 (5'-CTGGGAAGATTATCTAGCACATTAATAC-3'); DMAR72 (5'-CATAACGTTAAACTGTCTAAAGGG-3'). PCR products were purified from agarose gel using a QIAquick gel extraction kit from QIAGEN following the manufacturer's instructions (Chatsworth, CA) and the DNA insert were sequenced (Taq Dye Deoxy Terminator Cycle Sequencing kit, ABI, Foster City, CA). The predicted amino acid sequences from strains ATCC12384 (SEQ ID NO:2), LSPQ2699(ATCC19615) (SEQ ID NO:4), SPY57 (SEQ ID NO:6), and B514 (SEQ ID NO:8) were respectively presented in the following figures 2, 4, 6, and 8.

The figures 17 and 18 respectively depict the consensus nucleotide and predicted amino acid sequences established for S. pyogenes BVH-P1. In addition to the sequences presented herewith, the BVH-P1 gene sequences from the genome sequencing project at the University of Oklahoma (serotype M1 S. pyogenes strain ATCC 70029 : <http://dnal1.chem.ou.edu/strep.html> ) and from (Kil et al. 1994. Infect. Immun. 62 :2440-2449 : GenBank accession number U09352) were also included. No function or role in the pathogenesis of the bacteria or protection against infection was described by Kil et al. for the sequence with GenBank accession number U09352. This latter sequence presented by Kil et al. was shown to be located upstream of a S.pyogenes 67kDa myosin-cross-reactive antigen.

Pairwise comparison of the BVH-P1 predicted protein sequences revealed between 95 to 100% identity with the exception of the BVH-P1 sequence obtained from GenBank under the accession number U09352. Pairwise comparison of that particular sequence

with the other five BVH-P1 sequences indicated identity between 87 to 91%. This lower homology can be explained by the presence of two regions (119-124 and 262-281) which are more divergent comparatively to the other BVH-P1 gene sequences. Beside these  
5 two regions in the BVH-P1 sequence obtained from GenBank under the accesssion number U09352, the BVH-P1 genes showed great similarity in overall organization.

### 10 EXAMPLE 3

This example illustrates the cloning of S. pyogenes protein gene in CMV plasmid pCMV-GH.

The DNA coding region of a S. pyogenes protein was inserted in  
15 phase downstream of a human growth hormone (hGH) gene which was under the transcriptional control of the cytomegalovirus (CMV) promotor in the plasmid vector pCMV-GH (Tang et al., Nature, 1992, 356 :152). The CMV promotor is a non functional plasmid in E. coli cells but is active upon administration of the  
20 plasmid in eukaryotic cells. The vector also incorporated the ampicillin resistance gene.

The coding region of BVH-P1 gene (SEQ ID NO:9) without its leader peptide region was amplified by PCR (DNA Thermal Cycler  
25 GeneAmp PCR system 2400 Perkin Elmer, San Jose, CA) from genomic DNA of serotype 3 S. pyogenes strain ATCC12384 using the following oligos that contained base extensions for the addition of restriction sites *Bam*HI (GGATCC) and *Sal*I (GTCGAC): DMAR24 (5'-TACCCGGATCCCCAAGAGTGGACACCACGATCGG-3'); DMAR25 (5'-  
30 GCGCTCGTCGACGCGTATCTCAGCCTCTTATAGGGC-3'). The PCR product was purified from agarose gel using a QIAquick gel extraction kit from QIAGEN (Chatsworth, CA), digested with restriction enzymes (Pharmacia Canada Inc, Baie d'Urfe, Canada). The pCMV-GH vector (Laboratory of Dr. Stephen A. Johnston, Department of  
35 Biochemistry, The University of Texas, Dallas, Texas) was digested with *Bam*HI and *Sal*I and purified from agarose gel using

the QIAquick gel extraction kit from QIAGEN (Chatsworth, CA). The *Bam*HI-*Sal*I DNA fragments were ligated to the *Bam*HI-*Sal*I pCMV-GH vector to create the hGH-BVH-P1 fusion protein under the control of the CMV promoter. The ligated products were  
5 transformed into *E. coli* strain DH5 $\alpha$  [ $\phi$ 80dlacZ $\Delta$ M15  $\Delta$ (lacZYA-argF)U169 *endA*1 *recA*1 *hsdR*17(*r*<sub>K</sub>-*m*<sub>K</sub>+) *deoR* *thi*-1 *supE*44  $\lambda$ <sup>-</sup>*gyrA*96 *relA*1] (Gibco BRL, Gaithersburg, MD) according to the method of Simanis (Hanahan, D. DNA Cloning, 1985, D.M. Glover (ed), pp. 109-135). The recombinant pCMV plasmid was purified using a  
10 QIAGEN plasmid kit (Chatsworth, CA) and the nucleotide sequence of the DNA insert was verified by DNA sequencing.

#### EXAMPLE 4

15 This example illustrates the use of DNA to elicit an immune response to *S. pyogenes* antigens.

A group of 8 female BALB/c mice (Charles River, St-Constant, Québec, Canada) were immunized by intramuscular injection of 100  
20  $\mu$ l three times at two- or three-week intervals with 50  $\mu$ g of recombinant pCMV-GH encoding BVH-P1 gene in presence of 50  $\mu$ g of granulocyte-macrophage colony-stimulating factor (GM-CSF)-expressing plasmid pCMV-GH-GM-CSF (Laboratory of Dr. Stephen A. Johnston, Department of Biochemistry, The University of Texas,  
25 Dallas, Texas). As control, a group of mice were injected with 50  $\mu$ g of pCMV-GH in presence of 50  $\mu$ g of pCMV-GH-GM-CSF. Blood samples were collected from the orbital sinus prior to each immunization and seven days following the third injection and serum antibody responses were determined by ELISA using purified  
30 BVH-P1-His•Tag from SEQ ID NO:11 *S. pyogenes* recombinant protein as coating antigen.

## EXAMPLE 5

This example illustrates the production and purification of recombinant S. pyogenes BVH-P1 protein.

5 The recombinant pET-21d(+) plasmid with BVH-P1 gene corresponding to the SEQ ID NO:9 was used to transform by electroporation (Gene Pulser II apparatus, BIO-RAD Labs, Mississauga, Canada) E. coli strain BL21(DE3) (F<sup>-</sup>ompT hsdS<sub>B</sub> (r<sup>-</sup><sub>B</sub>m<sup>-</sup><sub>B</sub>) gal dcm (DE3)) (Novagen, Madison, WI). In this strain of E. coli, the T7  
10 promoter controlling expression of the recombinant protein is specifically recognized by the T7 RNA polymerase (present on the  $\lambda$ DE3 prophage) whose gene is under the control of the lac promoter which is inducible by isopropyl- $\beta$ -D-thio-galactopyranoside (IPTG). The transformant BL21(DE3)/rpET was  
15 grown at 37°C with agitation at 250 rpm in LB broth (peptone 10g/L, yeast extract 5g/L, NaCl 10g/L) containing 100  $\mu$ g of carbenicillin (Sigma-Aldrich Canada Ltd., Oakville, Canada) per ml until the A<sub>600</sub> reached a value of 0.6. In order to induce the production of S. pyogenes BVH-P1-His•Tag recombinant protein  
20 (from SEQ ID NO:10), the cells were incubated for 3 additional hours in the presence of IPTG at a final concentration of 1 mM. Induced cells from a 500 ml culture were pelleted by centrifugation and frozen at -70°C.

25 The purification of the recombinant proteins from the soluble cytoplasmic fraction of IPTG-induced BL21(DE3)/rpET21b(+) was done by affinity chromatography based on the properties of the His•Tag sequence (6 consecutive histidine residues) to bind to divalent cations (Ni<sup>2+</sup>) immobilized on the His•Bind metal  
30 chelation resin. Briefly, the pelleted cells obtained from a 500 mL culture induced with IPTG was resuspended in lysis buffer (20 mM Tris, 500 mM NaCl, 10 mM imidazole, pH 7.9) containing 1mM PMSF, sonicated and centrifuged at 12,000 X g for 20 min to remove debris. The supernatant was deposited on a Ni-NTA  
35 agarose column (Qiagen, Mississauga, Ontario, Canada). The S.

pyogenes BVH-P1-His•Tag recombinant protein (from SEQ ID NO:10) was eluted with 250 mM imidazole-500mM NaCl-20 mM Tris pH 7.9. The removal of the salt and imidazole from the sample was done by dialysis against PBS at 4°C. The quantities of recombinant protein obtained from the soluble fraction of E. coli was  
5 estimated by MicroBCA (Pierce, Rockford, Illinois).

## EXAMPLE 6

10 This example illustrates the accessibility to antibodies of the BVH-P1 protein at the surface of S. pyogenes strain.

Bacteria were grown in Tood Hewitt (TH) broth (Difco Laboratories, Detroit MI) with 0.5% Yeast extract (Difco  
15 Laboratories) and 0.5% peptone extract (Merck, Darmstadt, Germany) at 37°C in a 8% CO<sub>2</sub> atmosphere to give an OD<sub>490nm</sub> of 0.600 (~10<sup>8</sup> CFU/ml). Dilutions of anti-BVH-P1 or control sera were then added and allowed to bind to the cells, which were incubated for 2 h at 4°C. Samples were washed 4 times in blocking buffer  
20 [phosphate-buffered saline (PBS) containing 2% bovine serum albumin (BSA)], and then 1 ml of goat fluorescein (FITC)-conjugated anti-mouse IgG + IgM diluted in blocking buffer was added. After an additional incubation of 60 min. at room temperature, samples were washed 4 times in blocking buffer and  
25 fixed with 0.25 % formaldehyde in PBS buffer for 18-24 h at 4°C. Cells were washed 2 times in PBS buffer and resuspended in 500 µl of PBS buffer. Cells were kept in the dark at 4°C until analyzed by flow cytometry (Epics® XL; Beckman Coulter, Inc.). Flow cytometric analysis revealed that BVH-P1-specific  
30 antibodies efficiently recognized their corresponding surface exposed epitopes on both the homologous (ATCC12384; serotype3) and the heterologous (SPY57; seotype 1) S. pyogenes strains tested. It was determined that more than 90 % of the 10,000 S. pyogenes cells analyzed were labeled with the antibodies present  
35 in the BVH-MC1 specific anti-sera. These observations clearly



demonstrate that the BVH-P1 protein is accessible at the surface where it can be easily recognized by antibodies. Anti- S. pyogenes antibodies were shown to play an important role in the protection against S. pyogenes infection.

5

## EXAMPLE 7

This example illustrates the protection against fatal S. pyogenes infection induced by passive immunization of mice with rabbit hyper-immune sera.

10

New Zealand rabbits (Charles River laboratories, Montreal, Canada) were injected subcutaneously at multiple sites with approximately 50  $\mu$ g and 100  $\mu$ g of BVH-P1-His•Tag protein (from SEQ ID NO:10) that was produced and purified as described in Example 5 and adsorbed to Alhydrogel adjuvant (Superfos Biosector a/s). Rabbits were immunized three times at three-week intervals with the BVH-P1-His•Tag protein (from SEQ ID NO:10). Blood samples were collected three weeks after the third injection. The antibodies present in the serum were purified by precipitation using 40% saturated ammonium sulfate. Groups of 10 female CD-1 mice (Charles River) were injected intravenously with 500  $\mu$ l of purified serum collected either from BVH-P1-His•Tag (from SEQ ID NO:10) immunized rabbits or rabbits immunized with an unrelated control recombinant protein. Eighteen hours later the mice were challenged with approximately  $2 \times 10^7$  CFU of the type 3 S. pyogenes strain ATCC12384. Samples of the S. pyogenes challenge inoculum were plated on blood agar plates to determine the CFU and to verify the challenge dose. Deaths were recorded for a period of 5 days.

15

20

25

30

## EXAMPLE 8

This example illustrates the protection of mice against fatal S. pyogenes infection induced by immunization with BVH-P1 protein.

35

Groups of 8 female CD-1 mice (Charles River) were immunized subcutaneously three times at three-week intervals with 20  $\mu$ g of affinity purified S. pyogenes BVH-P1-His•Tag recombinant protein (from SEQ ID NO:10) in presence of 10  $\mu$ g of QuilA adjuvant (Cedarlane Laboratories Ltd, Hornby, Canada). or, as control, with QuilA adjuvant alone in PBS. Blood samples were collected from the orbital sinus on day 1, 22 and 43 prior to each immunization and seven days (day 50) following the third injection. Analysis by ELISA using purified recombinant BVH-P1 protein (from SEQ ID NO:10) clearly indicated that this protein is highly immunogenic in animals. Indeed reciprocal ELISA titers higher than  $10^6$  were determined for the mice immunized with this recombinant protein. Two weeks later the mice were challenged with approximately  $2 \times 10^7$  CFU of the type 3 S. pyogenes strain ATCC12384. Samples of the S. pyogenes challenge inoculum were plated on blood agar plates to determine the CFU and to verify the challenge dose. Deaths were recorded for a period of 5 days. Five out of the 8 (62%) mice immunized with three injections of 20  $\mu$ g of purified recombinant BVH-P1 (from SEQ ID NO:10) and QuilA adjuvant survived the bacterial challenge to only 2/7 (28%) in the control group.

Table 3. Immunization of CD-1 mice with purified recombinant BVH-P1 protein confers protection against subsequent challenge with S. pyogenes strain ATCC 12384

Groups	Survival of the mice challenged with <u>S. pyogenes</u> strain ATCC 12384 (Day after challenge: number of survivors/total number of mice challenged)				
	1	2	3	4	5
20 $\mu$ g of BVH-P1-His•Tag	8/8	8/8	7/8	6/8	5/8
Control	7/7	6/7	3/7	2/7	2/7

## SEQUENCE LISTING

<110> SHIRE BIOCHEM INC.  
MARTIN, Denis  
HAMEL, Josée  
BRODEUR, Bernard

<120> STREPTOCOCCUS PYOGENES ANTIGENS

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 gctgaagcaa tggggattga tgtgcatgtc ttaggagata ttaatcatat tgctaataatt 240  
 gacttaattt ttccagacac gatcctaaca gcaaactaca accaacacgg tcaggcaacg 300  
 actttgacgg ttcaagcacc tgcttctagt ccatctagcg ttagtcatgt acctagcagt 360  
 gagccattac cccaagcattc tgccacctct caaccgactg ttccatattggc accatctgcg 420  
 acaccatctg atgtcccaac gacaccattc gcatctgcaa agccagatag ttctgtgaca 480  
 gcgtcatctg agctcacatc gtcaacgaat gatgtttcga ctgagttgtc tagcgaatca 540  
 caaaagcagc cagaagtacc acaagaagca gttccaactc cttaaagcagc tgaaccgact 600  
 gaagtcgaac ctaagacaga catctcagaa gaccaactt cagctaatag gcctgtacct 660  
 aacgagagtg cttcagaaga agcttcttct gcggccccag cacaagctcc agcagaaaaa 720  
 gaagaaacct ctcatagttt aactgcgcca gcagcacaaa aagctgtagc tgacaccaca 780  
 agtggttgcaa cctcaaacgg cctttcttac gctccaaacc atgcctacaa tccaatgaat 840  
 gcagggtcttc aaccacaaac agcagccttc aaagaagaag tggttctctc ctttggtatt 900

acgtcattta gtggttaccg tccaggagat ccaggagatc atggtaaagg attagccatt 960

gactttatgg taccgggttag ctctacgctt ggtgatcaag ttgctcaata tgccattgac 1020  
 catatggcag agcgtgggtat ttcatacgtt atttggaac agcgattcta tgcgccattt 1080  
 gcaagtattt acggaccagc ctacacatgg aaccccatgc cagatcgcgg cagtattaca 1140  
 gaaaaccatt atgatcatgt tcatgtctcc tttaatgctt aa 1182

<210> 4

<211> 393

<212> PRT

<213> S. pyogenes

<400> 4

Met Ile Ile Thr Lys Lys Ser Leu Phe Val Thr Ser Val Ala Leu Ser  
 1 5 10 15  
 Leu Ala Pro Leu Ala Thr Ala Gln Ala Gln Glu Trp Thr Pro Arg Ser  
 20 25 30  
 Val Thr Glu Ile Lys Ser Glu Leu Val Leu Val Asp Asn Val Phe Thr  
 35 40 45  
 Tyr Ile Val Lys Tyr Gly Asp Thr Leu Ser Thr Ile Ala Glu Ala Met  
 50 55 60  
 Gly Ile Asp Val His Val Leu Gly Asp Ile Asn His Ile Ala Asn Ile  
 65 70 75 80  
 Asp Leu Ile Phe Pro Asp Thr Ile Leu Thr Ala Asn Tyr Asn Gln His  
 85 90 95  
 Gly Gln Ala Thr Thr Leu Thr Val Gln Ala Pro Ala Ser Ser Pro Ser  
 100 105 110  
 Ser Val Ser His Val Pro Ser Ser Glu Pro Leu Pro Gln Ala Ser Ala  
 115 120 125  
 Thr Ser Gln Pro Thr Val Pro Met Ala Pro Ser Ala Thr Pro Ser Asp  
 130 135 140  
 Val Pro Thr Thr Pro Phe Ala Ser Ala Lys Pro Asp Ser Ser Val Thr  
 145 150 155 160  
 Ala Ser Ser Glu Leu Thr Ser Ser Thr Asn Asp Val Ser Thr Glu Leu  
 165 170 175  
 Ser Ser Glu Ser Gln Lys Gln Pro Glu Val Pro Gln Glu Ala Val Pro  
 180 185 190  
 Thr Pro Lys Ala Ala Glu Pro Thr Glu Val Glu Pro Lys Thr Asp Ile  
 195 200 205  
 Ser Glu Asp Pro Thr Ser Ala Asn Arg Pro Val Pro Asn Glu Ser Ala  
 210 215 220  
 Ser Glu Glu Ala Ser Ser Ala Ala Pro Ala Gln Ala Pro Ala Glu Lys  
 225 230 235 240  
 Glu Glu Thr Ser Gln Met Leu Thr Ala Pro Ala Ala Gln Lys Ala Val  
 245 250 255  
 Ala Asp Thr Thr Ser Val Ala Thr Ser Asn Gly Leu Ser Tyr Ala Pro  
 260 265 270  
 Asn His Ala Tyr Asn Pro Met Asn Ala Gly Leu Gln Pro Gln Thr Ala  
 275 280 285  
 Ala Phe Lys Glu Glu Val Ala Ser Ala Phe Gly Ile Thr Ser Phe Ser  
 290 295 300  
 Gly Tyr Arg Pro Gly Asp Pro Gly Asp His Gly Lys Gly Leu Ala Ile  
 305 310 315 320  
 Asp Phe Met Val Pro Val Ser Ser Thr Leu Gly Asp Gln Val Ala Gln  
 325 330 335  
 Tyr Ala Ile Asp His Met Ala Glu Arg Gly Ile Ser Tyr Val Ile Trp  
 340 345 350  
 Lys Gln Arg Phe Tyr Ala Pro Phe Ala Ser Ile Tyr Gly Pro Ala Tyr  
 355 360 365  
 Thr Trp Asn Pro Met Pro Asp Arg Gly Ser Ile Thr Glu Asn His Tyr  
 370 375 380

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Asp His Val His Val Ser Phe Asn Ala  
385 390

<210> 5  
<211> 1170  
<212> DNA  
<213> S. pyogenes

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<400> 5
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gcgacagcgc aggcacaaga gtggacacca cgatcggtta cagaaatcaa gtctgaactc      120
gtcctagttg ataatgtttt tacttatact gtaaaatacg gtgacacttt aagcacaatt      180
gctgaagcaa tggggattga tgtgcatgtc ttaggagata ttaatcatat tgctaattatt      240
gacctaattt ttccagacac gatcctaaca gcaaactaca atcaacacgg tcaggcaacg      300
aatttgacgg ttcaagcacc tgcttctagt ccagctagcg ttagtcatgt acctagcagt      360
gagccattac cccaagcatc tgccacctct caaccgactg ttcttatggc accacctgcg      420
acaccatctg atgtcccaac gacaccattc gcatctgcaa agccagatag ttctgtgaca      480
gcgtcatctg agctcacatc gtcaacgaat gatgtttcga ctgagttgtc tagcgaatca      540
caaaagcagc cagaagtacc acaagaagca gttccaactc ctaaagcagc tgaaacgact      600
gaagtgcgaac ctaagacaga catctcagaa gccccaaactt cagctaatag gcctgtacct      660
aacgagagtg cttcagaaga agtttcttct gcggccccag cacaagcccc agcagaaaaa      720
gaagaaacct ctgcgccagc agcacaaaaa gctgtagctg acaccacaag tgttgcaacc      780
tcaaatggcc tttcttacgc tccaaacccat gcctacaatc caatgaatgc agggcttcaa      840
ccacaacacg cagccttcaa agaagaagtg gcttctgcct ttggtattac gtcatttagt      900
ggttaccgct caggtgatcc aggagatcat ggtaaagggt tggccattga ttttatggtg      960
cctgaaaatt ctgctcttgg tgatcaagtt gctcaatatg ccattgacca tatggcagag     1020
cgtgggtatt catacgttat ttggaaacag cgattctatg cgccatttgc aagtatttac     1080
ggaccagcct acacatggaa ccccatgcc a gatcgcgcca gtattacaga aaaccattat     1140
gatcatgttc atgtctcctt taatgcttaa                                     1170

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<210> 6  
<211> 389  
<212> PRT  
<213> S. pyogenes

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<400> 6
Met Ile Ile Thr Lys Lys Ser Leu Phe Val Thr Ser Val Ala Leu Ser
1      5      10      15
Leu Val Pro Leu Ala Thr Ala Gln Ala Gln Glu Trp Thr Pro Arg Ser
20     25     30
Val Thr Glu Ile Lys Ser Glu Leu Val Leu Val Asp Asn Val Phe Thr
35     40     45
Tyr Thr Val Lys Tyr Gly Asp Thr Leu Ser Thr Ile Ala Glu Ala Met
50     55     60
Gly Ile Asp Val His Val Leu Gly Asp Ile Asn His Ile Ala Asn Ile
65     70     75     80
Asp Leu Ile Phe Pro Asp Thr Ile Leu Thr Ala Asn Tyr Asn Gln His
85     90     95
Gly Gln Ala Thr Asn Leu Thr Val Gln Ala Pro Ala Ser Ser Pro Ala
100    105    110
Ser Val Ser His Val Pro Ser Ser Glu Pro Leu Pro Gln Ala Ser Ala
115    120    125
Thr Ser Gln Pro Thr Val Pro Met Ala Pro Pro Ala Thr Pro Ser Asp
130    135    140
Val Pro Thr Thr Pro Phe Ala Ser Ala Lys Pro Asp Ser Ser Val Thr
145    150    155    160
Ala Ser Ser Glu Leu Thr Ser Ser Thr Asn Asp Val Ser Thr Glu Leu
165    170    175
Ser Ser Glu Ser Gln Lys Gln Pro Glu Val Pro Gln Glu Ala Val Pro
180    185    190
Thr Pro Lys Ala Ala Glu Thr Thr Glu Val Glu Pro Lys Thr Asp Ile
195    200    205

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Ser Glu Ala Pro Thr Ser Ala Asn Arg Pro Val Pro Asn Glu Ser Ala  
 210 215 220  
 Ser Glu Glu Val Ser Ser Ala Ala Pro Ala Gln Ala Pro Ala Glu Lys  
 225 230 235 240  
 Glu Glu Thr Ser Ala Pro Ala Ala Gln Lys Ala Val Ala Asp Thr Thr  
 245 250 255  
 Ser Val Ala Thr Ser Asn Gly Leu Ser Tyr Ala Pro Asn His Ala Tyr  
 260 265 270  
 Asn Pro Met Asn Ala Gly Leu Gln Pro Gln Thr Ala Ala Phe Lys Glu  
 275 280 285  
 Glu Val Ala Ser Ala Phe Gly Ile Thr Ser Phe Ser Gly Tyr Arg Pro  
 290 295 300  
 Gly Asp Pro Gly Asp His Gly Lys Gly Leu Ala Ile Asp Phe Met Val  
 305 310 315 320  
 Pro Glu Asn Ser Ala Leu Gly Asp Gln Val Ala Gln Tyr Ala Ile Asp  
 325 330 335  
 His Met Ala Glu Arg Gly Ile Ser Tyr Val Ile Trp Lys Gln Arg Phe  
 340 345 350  
 Tyr Ala Pro Phe Ala Ser Ile Tyr Gly Pro Ala Tyr Thr Trp Asn Pro  
 355 360 365  
 Met Pro Asp Arg Gly Ser Ile Thr Glu Asn His Tyr Asp His Val His  
 370 375 380  
 Val Ser Phe Asn Ala  
 385

&lt;210&gt; 7

&lt;211&gt; 1149

&lt;212&gt; DNA

&lt;213&gt; S. pyogenes

&lt;400&gt; 7

atgattatta	ctaaaaagag	cttatttgtg	acaagtgtcg	ctttgtcggt	agcacctttg	60
gcgacagcgc	aggcacaaga	gtggacacca	cgatcgggta	cagaaatcaa	gtctgaactc	120
gtcctagttg	ataatgtttt	tacttatata	gtaaaatacg	gtgacacttt	aagcacaatt	180
gctgaagcaa	tggggattga	tgtgcatgtc	ttaggagata	ttaatcatat	tgctaattatt	240
gacttaattt	ttccagacac	gatacctaaca	gcaaactaca	atcaacacgg	tcaggcaacg	300
actttgacgg	ttcaagcacc	tgcttctagt	ccagctagcg	ttagtcatgt	acctagcagt	360
gagccattac	cccaagcatt	tgccacctct	caaccgactg	ttcctatggc	accatctgcg	420
acaccattag	catctgcaaa	gccagatagt	tctgtgacag	cgatcatctg	gctcacatcg	480
tcaacgaatg	atgttttcgac	tgagtctgtc	agcgaatcac	aaaagcagcc	agaagtacca	540
caagaagcag	ttccaactcc	taaagcagct	gaaacgactg	aagtcgaacc	taagacagac	600
atctcagaag	acccaacttc	agctaatagg	cctgtaccta	acgagagtgc	ttcagaagaa	660
gtttcttctg	cggccccagc	acaagcccca	gcagaaaaag	aagaaacctc	tgcgccagca	720
gcacaaaaag	ctgtagctga	caccacaagt	gttgcaacct	caaacggcct	ttcttacgct	780
ccaaaccatg	cctacaatcc	aatgaatgca	gggcttcaac	cacaaacagc	agccttcaaa	840
gaagaagtgg	cttctgcctt	tggtattacg	tcattttagt	gttaccgtcc	agggtgacca	900
ggagatcatg	gtaaagggtt	ggccattgat	tttatgggtg	ctgaaaattc	tgctcttggt	960
gatcaagttg	ctcaatatgc	cattgaccat	atggcagagc	gtgggtatttc	atagcttatt	1020
tggaaacagc	gattctatgc	gccatttgca	agtattttac	gaccagctta	cacatggaac	1080
cccatgccag	atcgcggcag	tattacagaa	aaccattatg	atcatgttca	tgtctccttt	1140
aatgcttaa						1149

&lt;210&gt; 8

&lt;211&gt; 382

&lt;212&gt; PRT

&lt;213&gt; S. pyogenes

&lt;400&gt; 8

Met Ile Ile Thr Lys Lys Ser Leu Phe Val Thr Ser Val Ala Leu Ser  
 1 5 10 15  
 Leu Ala Pro Leu Ala Thr Ala Gln Ala Gln Glu Trp Thr Pro Arg Ser  
 20 25 30

Val Thr Glu Ile Lys Ser Glu Leu Val Leu Val Asp Asn Val Phe Thr  
 35 40 45  
 Tyr Thr Val Lys Tyr Gly Asp Thr Leu Ser Thr Ile Ala Glu Ala Met  
 50 55 60  
 Gly Ile Asp Val His Val Leu Gly Asp Ile Asn His Ile Ala Asn Ile  
 65 70 75 80  
 Asp Leu Ile Phe Pro Asp Thr Ile Leu Thr Ala Asn Tyr Asn Gln His  
 85 90 95  
 Gly Gln Ala Thr Thr Leu Thr Val Gln Ala Pro Ala Ser Ser Pro Ala  
 100 105 110  
 Ser Val Ser His Val Pro Ser Ser Glu Pro Leu Pro Gln Ala Ser Ala  
 115 120 125  
 Thr Ser Gln Pro Thr Val Pro Met Ala Pro Ser Ala Thr Pro Leu Ala  
 130 135 140  
 Ser Ala Lys Pro Asp Ser Ser Val Thr Ala Ser Ser Glu Leu Thr Ser  
 145 150 155 160  
 Ser Thr Asn Asp Val Ser Thr Glu Ser Ser Ser Glu Ser Gln Lys Gln  
 165 170 175  
 Pro Glu Val Pro Gln Glu Ala Val Pro Thr Pro Lys Ala Ala Glu Thr  
 180 185 190  
 Thr Glu Val Glu Pro Lys Thr Asp Ile Ser Glu Asp Pro Thr Ser Ala  
 195 200 205  
 Asn Arg Pro Val Pro Asn Glu Ser Ala Ser Glu Glu Val Ser Ser Ala  
 210 215 220  
 Ala Pro Ala Gln Ala Pro Ala Glu Lys Glu Glu Thr Ser Ala Pro Ala  
 225 230 235 240  
 Ala Gln Lys Ala Val Ala Asp Thr Thr Ser Val Ala Thr Ser Asn Gly  
 245 250 255  
 Leu Ser Tyr Ala Pro Asn His Ala Tyr Asn Pro Met Asn Ala Gly Leu  
 260 265 270  
 Gln Pro Gln Thr Ala Ala Phe Lys Glu Glu Val Ala Ser Ala Phe Gly  
 275 280 285  
 Ile Thr Ser Phe Ser Gly Tyr Arg Pro Gly Asp Pro Gly Asp His Gly  
 290 295 300  
 Lys Gly Leu Ala Ile Asp Phe Met Val Pro Glu Asn Ser Ala Leu Gly  
 305 310 315 320  
 Asp Gln Val Ala Gln Tyr Ala Ile Asp His Met Ala Glu Arg Gly Ile  
 325 330 335  
 Ser Tyr Val Ile Trp Lys Gln Arg Phe Tyr Ala Pro Phe Ala Ser Ile  
 340 345 350  
 Tyr Gly Pro Ala Tyr Thr Trp Asn Pro Met Pro Asp Arg Gly Ser Ile  
 355 360 365  
 Thr Glu Asn His Tyr Asp His Val His Val Ser Phe Asn Ala  
 370 375 380

&lt;210&gt; 9

&lt;211&gt; 1095

&lt;212&gt; DNA

&lt;213&gt; S. pyogenes

&lt;400&gt; 9

caagagtggga caccacgatac gggttacagaa atcaagtcctg aactcgtcct agttgataat	60
gtttttacttt atactgtaaa atacggtgac actttaagca caattgctga agcaatggga	120
attgatgtgc atgtcttagg agatattaat catattgcta atattgactt aatttttcca	180
gacacgatcc taacagccaa ctacaaccaa cacggctcagg caacgacttt gacggttcaa	240
gcgcctgctt ctagtccagc tagcgttagt catgtacctg gcagtgagcc attaccccaa	300
gcacttgcca cctctcaatc gactgttcct atggcaccat ctgcgacacc atctgatgtc	360
ccaacgacac cattcgcatc tgcaaaagcca gatagttctg tgacagcgtc atctgagctc	420
acatcgtcaa cgaatgatgt ttcgactgag ttgtctagcg aatcacaaaa gcagccagaa	480
gtaccacaag aagcagttcc aactcctaaa gcagctgaaa cgactgaagt cgaacctaa	540
acagacatct cagaggattc aacttcagct aataggcctg tacctaacga gagtgttca	600
gaagaagttt cttctgcggc cccagcacia gcccagcag aaaaagaaga aacctctgcg	660



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ccagcagcac aaaaagctgt agctgacacc acaagtgttg caacctcaaa tggcctttct 720
tacgtcccaa accatgccta caatccaatg aatgcagggc ttcaaccaca aacagcagcc 780
ttcaaagaag aagtggcttc tgcctttggt attacgtcat ttagtggtta ccgtccaggt 840
gatccaggag atcatggtaa aggtttggcc attgatttta tggcgcctga aaattctgct 900
cttggatgat aagttgctca atatgccatt gaccatatgg cagagcgtgg tatttcatac 960
gttatttgga aacagcgatt ctatgcgcca tttgcaagta tttacggacc agcctacaca 1020
tggaacccca tgccagatcg cggcagtatt acagaaaacc attatgatca tgttcatgtc 1080
tcctttaatg cttaa                                     1095

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&lt;210&gt; 10

&lt;211&gt; 364

&lt;212&gt; PRT

&lt;213&gt; S. pyogenes

&lt;400&gt; 10

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Gln Glu Trp Thr Pro Arg Ser Val Thr Glu Ile Lys Ser Glu Leu Val
1          5          10          15
Leu Val Asp Asn Val Phe Thr Tyr Thr Val Lys Tyr Gly Asp Thr Leu
20          25          30
Ser Thr Ile Ala Glu Ala Met Gly Ile Asp Val His Val Leu Gly Asp
35          40          45
Ile Asn His Ile Ala Asn Ile Asp Leu Ile Phe Pro Asp Thr Ile Leu
50          55          60
Thr Ala Asn Tyr Asn Gln His Gly Gln Ala Thr Thr Leu Thr Val Gln
65          70          75          80
Ala Pro Ala Ser Ser Pro Ala Ser Val Ser His Val Pro Ser Ser Glu
85          90          95
Pro Leu Pro Gln Ala Ser Ala Thr Ser Gln Ser Thr Val Pro Met Ala
100         105         110
Pro Ser Ala Thr Pro Ser Asp Val Pro Thr Thr Pro Phe Ala Ser Ala
115         120         125
Lys Pro Asp Ser Ser Val Thr Ala Ser Ser Glu Leu Thr Ser Ser Thr
130         135         140
Asn Asp Val Ser Thr Glu Leu Ser Ser Glu Ser Gln Lys Gln Pro Glu
145         150         155         160
Val Pro Gln Glu Ala Val Pro Thr Pro Lys Ala Ala Glu Thr Thr Glu
165         170         175
Val Glu Pro Lys Thr Asp Ile Ser Glu Asp Ser Thr Ser Ala Asn Arg
180         185         190
Pro Val Pro Asn Glu Ser Ala Ser Glu Glu Val Ser Ser Ala Ala Pro
195         200         205
Ala Gln Ala Pro Ala Glu Lys Glu Glu Thr Ser Ala Pro Ala Ala Gln
210         215         220
Lys Ala Val Ala Asp Thr Thr Ser Val Ala Thr Ser Asn Gly Leu Ser
225         230         235         240
Tyr Ala Pro Asn His Ala Tyr Asn Pro Met Asn Ala Gly Leu Gln Pro
245         250         255
Gln Thr Ala Ala Phe Lys Glu Glu Val Ala Ser Ala Phe Gly Ile Thr
260         265         270
Ser Phe Ser Gly Tyr Arg Pro Gly Asp Pro Gly Asp His Gly Lys Gly
275         280         285
Leu Ala Ile Asp Phe Met Val Pro Glu Asn Ser Ala Leu Gly Asp Gln
290         295         300
Val Ala Gln Tyr Ala Ile Asp His Met Ala Glu Arg Gly Ile Ser Tyr
305         310         315         320
Val Ile Trp Lys Gln Arg Phe Tyr Ala Pro Phe Ala Ser Ile Tyr Gly
325         330         335
Pro Ala Tyr Thr Trp Asn Pro Met Pro Asp Arg Gly Ser Ile Thr Glu
340         345         350
Asn His Tyr Asp His Val His Val Ser Phe Asn Ala
355         360

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&lt;210&gt; 11

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&lt;211&gt; 1106

&lt;212&gt; DNA

<213> *S. pyogenes*

&lt;400&gt; 11

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caagagtggg caccacgata gggtacagaa atcaagtctg aactcgctcct agttgataat      60
gtttttactt atatatgaaa atacgggtgac actttaagca caattgctga agcaatgggg      120
attgatgtgc atgtcttagg agatattaat catattgcta atattgactt aatttttcca      180
gacacgatcc taacagcaaa ctacaaccaa caccggtcagg caacgacttt gacgggtcaa      240
gcacctgctt ctagtccatc tagcgttagt catgtaccta gcagtgaagg attaccctaa      300
gcatctgcca cctctcaacc gactgttctt atggcaccat ctgcgacacc atctgatgtc      360
ccaacgacac cattcgcatc tgcaaagcca gatagtcttg tgacagcgtc atctgagctc      420
acatcgtaaa cgaatgatgt ttcgactgag ttgtctagcg aatcacaaaa gcagccagaa      480
gtaccacaag aagcagttcc aactcctaaa gcagctgaac cgactgaagt cgaacctaaag      540
acagacatct cagaagaccc aacttcagct aataggcctg acctaacgag agtgcttcag      600
aagaagcttc ttctgcggcc ccagcacaag ctccagcaga aaaagaagaa acctctcaga      660
tgtaactgc gccagcagca caaaaagctg tagctgacac cacaagtgtt gcaacctcaa      720
acggcctttt ttacgctcca aaccatgcct acaatccaat gaatgcaggg cttcaaccac      780
aaacagcagc cttcaagaaa gaagtggctt ctgcctttgg tattacgtca tttagtgggt      840
accgtccagg agatccagga gatcatggta aaggattagc cattgacttt atgggtaccg      900
ttagctctac gcttggtgat caagttgctc aatatgccat tgaccatatg gcagagcgtg      960
gtatttcata cgttatttgg aaacagcgat tctatgcgcc atttgcaagt atttacggac     1020
cagcctacac atggaacccc atgccagatc gcggcagtat tacagaaaac cattatgata     1080
atgttcattg ctcctttaat gcttaa                                     1106

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&lt;210&gt; 12

&lt;211&gt; 368

&lt;212&gt; PRT

<213> *S. pyogenes*

&lt;400&gt; 12

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Gln Glu Trp Thr Pro Arg Ser Val Thr Glu Ile Lys Ser Glu Leu Val
 1             5             10             15
Leu Val Asp Asn Val Phe Thr Tyr Ile Val Lys Tyr Gly Asp Thr Leu
 20             25             30
Ser Thr Ile Ala Glu Ala Met Gly Ile Asp Val His Val Leu Gly Asp
 35             40             45
Ile Asn His Ile Ala Asn Ile Asp Leu Ile Phe Pro Asp Thr Ile Leu
 50             55             60
Thr Ala Asn Tyr Asn Gln His Gly Gln Ala Thr Thr Leu Thr Val Gln
 65             70             75             80
Ala Pro Ala Ser Ser Pro Ser Ser Val Ser His Val Pro Ser Ser Glu
 85             90             95
Pro Leu Pro Gln Ala Ser Ala Thr Ser Gln Pro Thr Val Pro Met Ala
100            105            110
Pro Ser Ala Thr Pro Ser Asp Val Pro Thr Thr Pro Phe Ala Ser Ala
115            120            125
Lys Pro Asp Ser Ser Val Thr Ala Ser Ser Glu Leu Thr Ser Ser Thr
130            135            140
Asn Asp Val Ser Thr Glu Leu Ser Ser Glu Ser Gln Lys Gln Pro Glu
145            150            155            160
Val Pro Gln Glu Ala Val Pro Thr Pro Lys Ala Ala Glu Pro Thr Glu
165            170            175
Val Glu Pro Lys Thr Asp Ile Ser Glu Asp Pro Thr Ser Ala Asn Arg
180            185            190
Pro Val Pro Asn Glu Ser Ala Ser Glu Glu Ala Ser Ser Ala Ala Pro
195            200            205
Ala Gln Ala Pro Ala Glu Lys Glu Glu Thr Ser Gln Met Leu Thr Ala
210            215            220
Pro Ala Ala Gln Lys Ala Val Ala Asp Thr Thr Ser Val Ala Thr Ser
225            230            235            240
Asn Gly Leu Ser Tyr Ala Pro Asn His Ala Tyr Asn Pro Met Asn Ala
245            250            255

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Gly Leu Gln Pro Gln Thr Ala Ala Phe Lys Glu Glu Val Ala Ser Ala  
 260 265 270  
 Phe Gly Ile Thr Ser Phe Ser Gly Tyr Arg Pro Gly Asp Pro Gly Asp  
 275 280 285  
 His Gly Lys Gly Leu Ala Ile Asp Phe Met Val Pro Val Ser Ser Thr  
 290 295 300  
 Leu Gly Asp Gln Val Ala Gln Tyr Ala Ile Asp His Met Ala Glu Arg  
 305 310 315 320  
 Gly Ile Ser Tyr Val Ile Trp Lys Gln Arg Phe Tyr Ala Pro Phe Ala  
 325 330 335  
 Ser Ile Tyr Gly Pro Ala Tyr Thr Trp Asn Pro Met Pro Asp Arg Gly  
 340 345 350  
 Ser Ile Thr Glu Asn His Tyr Asp His Val His Val Ser Phe Asn Ala  
 355 360 365

&lt;210&gt; 13

&lt;211&gt; 1095

&lt;212&gt; DNA

&lt;213&gt; S. pyogenes

&lt;400&gt; 13

```

caagagtgga caccacgatac gggtacagaa atcaagtctg aactcgtcct agttgataat      60
gtttttactt atactgtaaa atacggtgac actttaagca caattgctga agcaatgggg      120
attgatgtgc atgtcttagg agatattaat catattgcta atattgacct aatttttcca      180
gacacgatcc taacagcaaa ctacaatcaa cacggtcagg caacgaattt gacggttcaa      240
gcacctgctt ctagtccagc tagcgtagt catgtaccta gcagtgagcc attaccccaa      300
gcatctgcca cctctcaacc gactgttcct atggcaccac ctgacgacacc atctgatgtc      360
ccaacgacac cattcgcatc tgcaaagcca gatagtcttg tgacagcgctc atctgagctc      420
acatcgtaaa cgaatgatgt ttcgactgag ttgtctagcg aatcacaaaa gcagccagaa      480
gtaccacaag aagcagttcc aactcctaaa gcagctgaaa cgactgaagt cgaacctaaag      540
acagacatct cagaagcccc aacttcagct aataggcctg tacctaacga gagtgtctca      600
gaagaagttt cttctgcggc cccagcacia gcccagcag aaaaagaaga aacctctgcg      660
ccagcagcac aaaaagctgt agctgacacc acaagtgttg caacctcaaa tggcctttct      720
tacgtcccaa accatgccta caatccaatg aatgcagggc ttcaaccaca aacagcagcc      780
ttcaaagaag aagtggcttc tgcttttggt attacgtcat ttagtgggta ccgtccagggt      840
gatccaggag atcatggtaa aggtttggcc attgatttta tgggtgcctga aaattctgct      900
cttgggtgatc aagttgctca atatgccatt gaccatattg cagagcgtgg tatttcatac      960
gttatttggg aacagcgatt ctatgcgcca tttgcaagta ttacgggacc agcctacaca     1020
tggaacccca tgccagatcg cggcagttat acagaaaacc attatgatca tgttcatgtc     1080
tcctttaatg cttaa                                     1095

```

&lt;210&gt; 14

&lt;211&gt; 364

&lt;212&gt; PRT

&lt;213&gt; S. pyogenes

&lt;400&gt; 14

Gln Glu Trp Thr Pro Arg Ser Val Thr Glu Ile Lys Ser Glu Leu Val  
 1 5 10 15  
 Leu Val Asp Asn Val Phe Thr Tyr Thr Val Lys Tyr Gly Asp Thr Leu  
 20 25 30  
 Ser Thr Ile Ala Glu Ala Met Gly Ile Asp Val His Val Leu Gly Asp  
 35 40 45  
 Ile Asn His Ile Ala Asn Ile Asp Leu Ile Phe Pro Asp Thr Ile Leu  
 50 55 60  
 Thr Ala Asn Tyr Asn Gln His Gly Gln Ala Thr Asn Leu Thr Val Gln  
 65 70 75 80  
 Ala Pro Ala Ser Ser Pro Ala Ser Val Ser His Val Pro Ser Ser Glu  
 85 90 95  
 Pro Leu Pro Gln Ala Ser Ala Thr Ser Gln Pro Thr Val Pro Met Ala  
 100 105 110  
 Pro Pro Ala Thr Pro Ser Asp Val Pro Thr Thr Pro Phe Ala Ser Ala  
 115 120 125

Lys Pro Asp Ser Ser Val Thr Ala Ser Ser Glu Leu Thr Ser Ser Thr  
 130 135 140  
 Asn Asp Val Ser Thr Glu Leu Ser Ser Glu Ser Gln Lys Gln Pro Glu  
 145 150 155 160  
 Val Pro Gln Glu Ala Val Pro Thr Pro Lys Ala Ala Glu Thr Thr Glu  
 165 170 175  
 Val Glu Pro Lys Thr Asp Ile Ser Glu Ala Pro Thr Ser Ala Asn Arg  
 180 185 190  
 Pro Val Pro Asn Glu Ser Ala Ser Glu Glu Val Ser Ser Ala Ala Pro  
 195 200 205  
 Ala Gln Ala Pro Ala Glu Lys Glu Glu Thr Ser Ala Pro Ala Ala Gln  
 210 215 220  
 Lys Ala Val Ala Asp Thr Thr Ser Val Ala Thr Ser Asn Gly Leu Ser  
 225 230 235 240  
 Tyr Ala Pro Asn His Ala Tyr Asn Pro Met Asn Ala Gly Leu Gln Pro  
 245 250 255  
 Gln Thr Ala Ala Phe Lys Glu Glu Val Ala Ser Ala Phe Gly Ile Thr  
 260 265 270  
 Ser Phe Ser Gly Tyr Arg Pro Gly Asp Pro Gly Asp His Gly Lys Gly  
 275 280 285  
 Leu Ala Ile Asp Phe Met Val Pro Glu Asn Ser Ala Leu Gly Asp Gln  
 290 295 300  
 Val Ala Gln Tyr Ala Ile Asp His Met Ala Glu Arg Gly Ile Ser Tyr  
 305 310 315 320  
 Val Ile Trp Lys Gln Arg Phe Tyr Ala Pro Phe Ala Ser Ile Tyr Gly  
 325 330 335  
 Pro Ala Tyr Thr Trp Asn Pro Met Pro Asp Arg Gly Ser Ile Thr Glu  
 340 345 350  
 Asn His Tyr Asp His Val His Val Ser Phe Asn Ala  
 355 360

&lt;210&gt; 15

&lt;211&gt; 1074

&lt;212&gt; DNA

&lt;213&gt; S. pyogenes

&lt;400&gt; 15

caagagtggg	caccacgatac	ggttacagaa	atcaagtctg	aactcgtcct	agttgataat	60
gtttttactt	atacagtaaa	atacggtgac	actttaagca	caattgctga	agcaatgggg	120
attgatgtgc	atgtcttagg	agatattaat	catattgcta	atattgactt	aatttttcca	180
gacacgatcc	taacagcaaa	ctacaatcaa	cacggtcagg	caacgacttt	gacgggttcaa	240
gcacctgctt	ctagtccagc	tagecgttagt	catgtaccta	gcagtgagcc	attaccccaa	300
gcacatgcga	cctctcaacc	gactgttctt	atggcaccat	ctgcgacacc	attagcatct	360
gcaaaagccag	atagttctgt	gacagcgtca	tctgagctca	catcgtcaac	gaatgatgtt	420
tcgactgagt	cgtctagcga	atcacaaaag	cagccagaag	taccacaaga	agcagttcca	480
actcctaaag	cagctgaaac	gactgaagtc	gaacctaaag	cagacatctc	agaagaccca	540
acttcagcta	ataggcctgt	acctaacgag	agtgtctcag	aagaagtttc	ttctgctggc	600
ccagcacaag	ccccagcaga	aaaagaagaa	acctctgcgc	cagcagcaca	aaaagctgta	660
gctgacacca	caagtgttgc	aacctcaaac	ggcctttctt	acgctccaaa	ccatgcctac	720
aatccaatga	atgcagggct	tcaaccacaa	acagcagcct	tcaaagaaga	agtggttctt	780
gcctttggta	ttacgtcatt	tagtggttac	cgtccagggtg	acccaggaga	tcattggtaaa	840
ggttttggcca	ttgattttat	gggtgcctgaa	aattctgtct	ttggtgatca	agttgctcaa	900
tatgccattg	accatatggc	agagcgtggg	atttcatacg	ttattttggaa	acagcgattc	960
tatgcgccat	ttgcaagtat	ttacggacca	gcttacacat	ggaaccccat	gccagatcgc	1020
ggcagtatta	cagaaaacca	ttatgatcat	gttcattgtct	cctttaatgc	ttaa	1074

&lt;210&gt; 16

&lt;211&gt; 357

&lt;212&gt; PRT

&lt;213&gt; S. pyogenes

&lt;400&gt; 16

Gln Glu Trp Thr Pro Arg Ser Val Thr Glu Ile Lys Ser Glu Leu Val  
 1 5 10 15  
 Leu Val Asp Asn Val Phe Thr Tyr Thr Val Lys Tyr Gly Asp Thr Leu  
 20 25 30  
 Ser Thr Ile Ala Glu Ala Met Gly Ile Asp Val His Val Leu Gly Asp  
 35 40 45  
 Ile Asn His Ile Ala Asn Ile Asp Leu Ile Phe Pro Asp Thr Ile Leu  
 50 55 60  
 Thr Ala Asn Tyr Asn Gln His Gly Gln Ala Thr Thr Leu Thr Val Gln  
 65 70 75 80  
 Ala Pro Ala Ser Ser Pro Ala Ser Val Ser His Val Pro Ser Ser Glu  
 85 90 95  
 Pro Leu Pro Gln Ala Ser Ala Thr Ser Gln Pro Thr Val Pro Met Ala  
 100 105 110  
 Pro Ser Ala Thr Pro Leu Ala Ser Ala Lys Pro Asp Ser Ser Val Thr  
 115 120 125  
 Ala Ser Ser Glu Leu Thr Ser Ser Thr Asn Asp Val Ser Thr Glu Ser  
 130 135 140  
 Ser Ser Glu Ser Gln Lys Gln Pro Glu Val Pro Gln Glu Ala Val Pro  
 145 150 155 160  
 Thr Pro Lys Ala Ala Glu Thr Thr Glu Val Glu Pro Lys Thr Asp Ile  
 165 170 175  
 Ser Glu Asp Pro Thr Ser Ala Asn Arg Pro Val Pro Asn Glu Ser Ala  
 180 185 190  
 Ser Glu Glu Val Ser Ser Ala Ala Pro Ala Gln Ala Pro Ala Glu Lys  
 195 200 205  
 Glu Glu Thr Ser Ala Pro Ala Ala Gln Lys Ala Val Ala Asp Thr Thr  
 210 215 220  
 Ser Val Ala Thr Ser Asn Gly Leu Ser Tyr Ala Pro Asn His Ala Tyr  
 225 230 235 240  
 Asn Pro Met Asn Ala Gly Leu Gln Pro Gln Thr Ala Ala Phe Lys Glu  
 245 250 255  
 Glu Val Ala Ser Ala Phe Gly Ile Thr Ser Phe Ser Gly Tyr Arg Pro  
 260 265 270  
 Gly Asp Pro Gly Asp His Gly Lys Gly Leu Ala Ile Asp Phe Met Val  
 275 280 285  
 Pro Glu Asn Ser Ala Leu Gly Asp Gln Val Ala Gln Tyr Ala Ile Asp  
 290 295 300  
 His Met Ala Glu Arg Gly Ile Ser Tyr Val Ile Trp Lys Gln Arg Phe  
 305 310 315 320  
 Tyr Ala Pro Phe Ala Ser Ile Tyr Gly Pro Ala Tyr Thr Trp Asn Pro  
 325 330 335  
 Met Pro Asp Arg Gly Ser Ile Thr Glu Asn His Tyr Asp His Val His  
 340 345 350  
 Val Ser Phe Asn Ala  
 355

&lt;210&gt; 17

&lt;211&gt; 1113

&lt;212&gt; DNA

&lt;213&gt; S. pneumonia

&lt;400&gt; 17

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atgaagaaaa gaatgttatt agcgtcaaca gtagccttgt catttgcccc agtattggca      60
actcaagcag aagaagttct ttggactgca cgtagtgttg agcaaatcca aaacgatttg      120
actaaaacgg acaacaaaac aagttatacc gtacagtatg gtgatacttt gagcaccatt      180
gcagaagcct tgggtgtaga tgtcacagtg cttgcgaatc tgaacaaaat cactaatatg      240
gacttgattt tcccagaaac tgttttgaca acgactgtca atgaagcaga agaagtaaca      300
gaagttgaaa tccaacacc tcaagcagac tctagtgaag aagtgacaac tgcgacagca      360
gatttgacca ctaatcaagt gaccgttgat gatcaaatg ttcagggttg agacctttct      420
caaccaattg cagaagttac aaagacagtg attgcttctg aagaagtggc accatctacg      480
ggcactttct gccagagga gcaaacgacc gaaacaactc gccagttga agaagcaact      540
cctcaggaaa cgactccagc tgagaagcag gaaacacaag caagccctca agctgcatca      600

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gcagtgggaag taactacaac aagttcagaa gcaaaagaag tagcatcatc aaatggagct 660
acagcagcag tttctactta tcaaccagaa gagacgaaaa taatttcaac aacttacgag 720
gctccagctg cgcccagatta tgctggactt gcagtagcaa aatctgaaaa tgcaggtctt 780
caaccacaaa cagctgcctt taaagaagaa attgctaact tgtttggcat tacatccttt 840
agtgggttatc gtccaggaga cagtggagat cacggaaaaag gtttggctat cgactttatg 900
gtaccagaac gttcagaatt aggggataag attgcggaat atgctattca aaatatggcc 960
agccgtggca ttagttacat catctggaaa caacgtttct atgctccatt cgatagcaaa 1020
tatgggccag ctaacacttg gaaccaatg ccagaccgtg gtagtgtgac agaaaatcac 1080
tatgatcacg ttcacgtttc aatgaatgga taa 1113

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&lt;210&gt; 18

&lt;211&gt; 370

&lt;212&gt; PRT

&lt;213&gt; S. pneumonia

&lt;400&gt; 18

```

Met Lys Lys Arg Met Leu Leu Ala Ser Thr Val Ala Leu Ser Phe Ala
1      5      10      15
Pro Val Leu Ala Thr Gln Ala Glu Glu Val Leu Trp Thr Ala Arg Ser
20      25      30
Val Glu Gln Ile Gln Asn Asp Leu Thr Lys Thr Asp Asn Lys Thr Ser
35      40      45
Tyr Thr Val Gln Tyr Gly Asp Thr Leu Ser Thr Ile Ala Glu Ala Leu
50      55      60
Gly Val Asp Val Thr Val Leu Ala Asn Leu Asn Lys Ile Thr Asn Met
65      70      75      80
Asp Leu Ile Phe Pro Glu Thr Val Leu Thr Thr Thr Val Asn Glu Ala
85      90      95
Glu Glu Val Thr Glu Val Glu Ile Gln Thr Pro Gln Ala Asp Ser Ser
100     105     110
Glu Glu Val Thr Thr Ala Thr Ala Asp Leu Thr Thr Asn Gln Val Thr
115     120     125
Val Asp Asp Gln Thr Val Gln Val Ala Asp Leu Ser Gln Pro Ile Ala
130     135     140
Glu Val Thr Lys Thr Val Ile Ala Ser Glu Glu Val Ala Pro Ser Thr
145     150     155     160
Gly Thr Ser Val Pro Glu Glu Gln Thr Thr Glu Thr Thr Arg Pro Val
165     170     175
Glu Glu Ala Thr Pro Gln Glu Thr Thr Pro Ala Glu Lys Gln Glu Thr
180     185     190
Gln Ala Ser Pro Gln Ala Ala Ser Ala Val Glu Val Thr Thr Thr Ser
195     200     205

Ser Glu Ala Lys Glu Val Ala Ser Ser Asn Gly Ala Thr Ala Ala Val
210     215     220
Ser Thr Tyr Gln Pro Glu Glu Thr Lys Ile Ile Ser Thr Thr Tyr Glu
225     230     235     240
Ala Pro Ala Ala Pro Asp Tyr Ala Gly Leu Ala Val Ala Lys Ser Glu
245     250     255
Asn Ala Gly Leu Gln Pro Gln Thr Ala Ala Phe Lys Glu Glu Ile Ala
260     265     270
Asn Leu Phe Gly Ile Thr Ser Phe Ser Gly Tyr Arg Pro Gly Asp Ser
275     280     285
Gly Asp His Gly Lys Gly Leu Ala Ile Asp Phe Met Val Pro Glu Arg
290     295     300
Ser Glu Leu Gly Asp Lys Ile Ala Glu Tyr Ala Ile Gln Asn Met Ala
305     310     315     320
Ser Arg Gly Ile Ser Tyr Ile Ile Trp Lys Gln Arg Phe Tyr Ala Pro
325     330     335
Phe Asp Ser Lys Tyr Gly Pro Ala Asn Thr Trp Asn Pro Met Pro Asp
340     345     350
Arg Gly Ser Val Thr Glu Asn His Tyr Asp His Val His Val Ser Met
355     360     365

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WO 02/04495

PCT/CA01/01001

Asn Gly  
: 370

<210> 19  
<211> 1183  
<212> DNA  
<213> S. pyogenes

<220>  
<221> misc\_difference  
<222> (428)...(448)  
<223> nnnnnnnnnnnnnnnnnnnnn can be ctgatgtccaacgacaccat  
or absent

<221> misc\_difference  
<222> (733)...(744)  
<223> nnnnnnnnnnnnnnnnnnnnn can be cagatgttaact or absent

<221> misc\_difference  
<222> (883)...(883)  
<223> n is g or absent

<221> misc\_difference  
<222> (943)...(943)  
<223> n is t or absent

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<400> 19
atgattatta ctaaaaagag yttattttgtg acaagtgtcg ctttgtcggtt agyacctttg      60
gcgacagcrc aggcacaaga gtggacacca cgatcggtta casaaatcaa gtctgaactc      120
gtcctagtgtg ataatgtttt tacttatayw gtaaaatacy gtgacacttt aagcacaatt      180
gctgaagcaa tgggrattga tgtgcatgtc ttaggagata ttaatcatat tgctaataatt      240
gacytaattt ttccagacac gatcctaaca gcmaactaca aycaacacgg tcaggcaacg      300
amtttgacgg ttcaagcrcc tgcttctagt ccakctagcg ttagtcatgt acctagcagt      360
gagccattac cccaagcatc tgccacctct caaycgactr ttcctatggc accayctgcg      420
acaccatnnn nnnnnnnnnn nnnnnnnntm gcactctgcaa agccagatag ttytgtgaca      480
gcgtcatctg agctcacatc rtcaacgaat gatgtttcga ctgagtygtc tagcgaatca      540
caaaagcagc cagaagtacg acaagaagca gwwccaactc ctaaagcagc tgaamssact      600
gaagtcgaac ctaagacaga catctcagar gmyycaactt cagctaatag gcctgtacct      660
aacgrragtg cttcagaaga agyttcttct gcggcccccag cacaagcycc agcagaaaaa      720
gaagaaacct ctnnnnnnnn nnnnngcgcca gcagcacaaa aagctgtagc tgacaccaca      780
agtgttgcaa cctcaaaygg cctttcttac gctccaaacc atgcctacaa tccaatgaat      840
gcaggggcttc aaccacaaaac agcagccttc aaagaagaag tgncttctgc ctttgggtatt      900
acgtcattta gtggttaccg tccaggwgay ccaggagatc atnggtaaag gwtttrgcat      960
tgaytttatg gtrcckgwwa rytctrckct tgggtgatcaa gttgctcaat atgccattga     1020
ccatatggca gassgtggtg ttccatacgt tatttggaaa cagcgattct atgcgccatt     1080
tgcaagtatc tacggaccag cytacacatg gaaccccatg ccagatcgcg gcagtattac     1140
agwwwcccat tatgatcatg ttcatgtctc ctttaatgct taa                        1183

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<210> 20  
<211> 393  
<212> PRT  
<213> S. pyogenes

<220>  
<221> VARIANT  
<222> (18)...(18)  
<223> Xaa = Ala or Val

<221> VARIANT  
<222> (50)...(50)  
<223> Xaa = Thr or Ile

<221> VARIANT

<222> (101)...(101),  
<223> Xaa = Thr or Asn

<221> VARIANT  
<222> (112)...(112)  
<223> Xaa = Ala or Ser

<221> VARIANT  
<222> (132)...(132)  
<223> Xaa = Pro or Ser

<221> VARIANT  
<222> (134)...(134)  
<223> Xaa = Val or Ile

<221> VARIANT  
<222> (139)...(139)  
<223> Xaa = Ser or Pro

<221> VARIANT  
<222> (143)...(149)  
<223> Xaa Xaa Xaa Xaa Xaa Xaa Xaa = Ser Asp Val Pro Thr  
Thr pro or absent

<221> VARIANT  
<222> (150)...(150)  
<223> Xaa = Phe or Leu

<221> VARIANT  
<222> (158)...(158)  
<223> Xaa = Ser or Phe

<221> VARIANT  
<222> (176)...(176)  
<223> Xaa = Leu or Ser

<221> VARIANT  
<222> (191)...(191)  
<223> Xaa = Val or Glu

<221> VARIANT  
<222> (199)...(199)  
<223> Xaa = Thr or Pro or Ser

<221> VARIANT  
<222> (211)...(211)  
<223> Xaa = Asp or Ala

<221> VARIANT  
<222> (212)...(212)  
<223> Xaa = Pro or Ser

<221> VARIANT  
<222> (222)...(222)  
<223> Xaa = Glu or Gly

<221> VARIANT  
<222> (228)...(228)  
<223> Xaa = Val or Ala

<221> VARIANT  
<222> (242)...(245)  
<223> Xaa Xaa Xaa Xaa = Glu thr Ser Gln or absent



<221> VARIANT  
<222> (246)...(246)  
<223> Xaa = Glu or Met

<221> VARIANT  
<222> (247)...(247)  
<223> Xaa = Thr or Leu

<221> VARIANT  
<222> (248)...(248)  
<223> Xaa = Ser or Thr

<221> VARIANT  
<222> (295)...(295)  
<223> Xaa = Ala or Leu

<221> VARIANT  
<222> (296)...(296)  
<223> Xaa = Ser or Leu

<221> VARIANT  
<222> (297)...(297)  
<223> Xaa = Ala or Pro

<221> VARIANT  
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<223> Xaa = Phe or Leu

<221> VARIANT  
<222> (299)...(299)  
<223> Xaa = Gly or Val

<221> VARIANT  
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<223> Xaa = Ile or Leu

<221> VARIANT  
<222> (301)...(301)  
<223> Xaa = Thr or Arg

<221> VARIANT  
<222> (302)...(302)  
<223> Xaa = Ser or His

<221> VARIANT  
<222> (303)...(303)  
<223> Xaa = Phe or Leu

<221> VARIANT  
<222> (304)...(304)  
<223> Xaa = Ser or Val

<221> VARIANT  
<222> (305)...(305)  
<223> Xaa = Gly or Val

<221> VARIANT  
<222> (306)...(306)  
<223> Xaa = Tyr or Thr

<221> VARIANT  
<222> (307)...(307)

<223> Xaa = Arg or Val

<221> VARIANT

<222> (308)...(308)

<223> Xaa = Pro or Gln

<221> VARIANT

<222> (309)...(309)

<223> Xaa = Gly or Glu

<221> VARIANT

<222> (310)...(310)

<223> Xaa = Asp or Ile

<221> VARIANT

<222> (311)...(311)

<223> Xaa = Pro or Gln

<221> VARIANT

<222> (312)...(312)

<223> Xaa = Gly or Glu

<221> VARIANT

<222> (313)...(313)

<223> Xaa = Asn or Ile

<221> VARIANT

<222> (314)...(314)

<223> Xaa = His or Ile

<221> VARIANT

<222> (326)...(326)

<223> Xaa = Glu or Val

<221> VARIANT

<222> (327)...(327)

<223> Xaa = Asn or Ser

<221> VARIANT

<222> (329)...(329)

<223> Xaa = Ala or Thr

<221> VARIANT

<222> (344)...(344)

<223> Xaa = Glu or Asp

<221> VARIANT

<222> (345)...(345)

<223> Xaa = Arg or Gly

<400> 20

Met	Ile	Ile	Thr	Lys	Lys	Ser	Leu	Phe	Val	Thr	Ser	Val	Ala	Leu	Ser
1				5					10					15	
Leu	Xaa	Pro	Leu	Ala	Thr	Ala	Gln	Ala	Gln	Glu	Trp	Thr	Pro	Arg	Ser
		20					25						30		
Val	Thr	Glx	Ile	Lys	Ser	Glu	Leu	Val	Leu	Val	Asp	Asn	Val	Phe	Thr
	35						40					45			
Tyr	Xaa	Val	Lys	Tyr	Gly	Asp	Thr	Leu	Ser	Thr	Ile	Ala	Glu	Ala	Met
	50					55				60					
Gly	Ile	Asp	Val	His	Val	Leu	Gly	Asp	Ile	Asn	His	Ile	Ala	Asn	Ile
65					70					75					80

```

Asp Leu Ile Phe Pro Asp Thr Ile Leu Thr Ala Asn Tyr Asn Gln His
      85                      90                      95
Gly Gln Ala Thr Xaa Leu Thr Val Gln Ala Pro Ala Ser Ser Pro Xaa
      100                    105                    110
Ser Val Ser His Val Pro Ser Ser Glu Pro Leu Pro Gln Ala Ser Ala
      115                    120                    125
Thr Ser Gln Xaa Thr Xaa Pro Met Ala Pro Xaa Ala Thr Pro Xaa Xaa
      130                    135                    140
Xaa Xaa Xaa Xaa Xaa Xaa Ala Ser Ala Lys Pro Asp Ser Xaa Val Thr
145                      150                      155                      160
Ala Ser Ser Glu Leu Thr Ser Ser Thr Asn Asp Val Ser Thr Glu Xaa
      165                    170                    175
Ser Ser Glu Ser Gln Lys Gln Pro Glu Val Pro Gln Glu Ala Xaa Pro
      180                    185                    190
Thr Pro Lys Ala Ala Glu Xaa Thr Glu Val Glu Pro Lys Thr Asp Ile
      195                    200                    205
Ser Glu Xaa Xaa Thr Ser Ala Asn Arg Pro Val Pro Asn Xaa Ser Ala
      210                    215                    220
Ser Glu Glu Xaa Ser Ser Ala Ala Pro Ala Gln Ala Pro Ala Glu Lys
225                      230                      235                      240
Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ala Pro Ala Ala Gln Lys Ala Val
      245                    250                    255
Ala Asp Thr Thr Ser Val Ala Thr Ser Asn Gly Leu Ser Tyr Ala Pro
      260                    265                    270
Asn His Ala Tyr Asn Pro Met Asn Ala Gly Leu Gln Pro Gln Thr Ala
      275                    280                    285
Ala Phe Lys Glu Glu Val Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
290                      295                      300
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Gly Lys Gly Leu Ala Ile
305                      310                      315                      320
Asp Phe Met Val Pro Xaa Xaa Ser Xaa Leu Gly Asp Gln Val Ala Gln
      325                    330                    335
Tyr Ala Ile Asp His Met Ala Xaa Xaa Gly Ile Ser Tyr Val Ile Trp
      340                    345                    350
Lys Gln Arg Phe Tyr Ala Pro Phe Ala Ser Ile Tyr Gly Pro Ala Tyr
      355                    360                    365
Thr Trp Asn Pro Met Pro Asp Arg Gly Ser Ile Thr Xaa Xaa His Tyr
370                      375                      380
Asp His Val His Val Ser Phe Asn Ala
385                      390

```

&lt;210&gt; 21

&lt;211&gt; 32

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; DMAR16 Oligonucleotide

&lt;400&gt; 21

caggccatgg agtggacacc acgatcggtt ac

32

&lt;210&gt; 22

&lt;211&gt; 37

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; DMAR17 Oligonucleotide

&lt;400&gt; 22

gccgctcgag agcattaaag gagacatgaa catgatac

37

<210> 23  
 <211> 25  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Signal peptide predicted from analysis of SEQ ID  
 NO:2

<400> 23  
 Met Ile Ile Thr Lys Lys Ser Leu Phe Val Thr Ser Val Ala Leu Ser  
 1 5 10 15  
 Leu Ala Pro Leu Ala Thr Ala Gln Ala  
 20 25

<210> 24  
 <211> 5  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <221> VARIANT  
 <222> (3)...(3)  
 <223> Xaa = Any Amino Acid

<223> Cell wall anchoring motif

<400> 24  
 Leu Pro Xaa Thr Gly  
 1 5

<210> 25  
 <211> 6  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> IgA binding motif

<400> 25  
 Met Leu Lys Lys Ile Glu  
 1 5

<210> 26  
 <211> 28  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> DMAR69 oligonucleotide

<400> 26  
 ctgggaagat tatctagcac attaatac

28

<210> 27  
 <211> 25  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> DMAR72 oligonucleotide

<400> 27

cataacgtta aaactgtcta aaggg

25

<210> 28

<211> 34

<212> DNA

<213> Artificial Sequence

<220>

<223> DMAR24 oligonucleotide

<400> 28

taccctggatc cccaagagtg gacaccacga tcgg

34

<210> 29

<211> 36

<212> DNA

<213> Artificial Sequence

<220>

<223> DMAR25 oligonucleotide

<400> 29

gcgctcgtcg acgcgtatct cagcctctta tagggc

36

What is claimed is:

1. An isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide having a sequence chosen from: SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 20 or fragments, analogues or derivatives thereof.
2. A polynucleotide according to claim 1, wherein said polynucleotide encodes a polypeptide having at least 95% identity to the second polypeptide.
3. An isolated polynucleotide encoding a polypeptide having at least 70% identity to a second polypeptide having a sequence chosen from: SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16 or 20.
4. A polynucleotide according to claim 3, wherein said polynucleotide encodes a polypeptide having at least 95% identity to the second polypeptide.
5. An isolated polynucleotide encoding a polypeptide capable of generating antibodies having binding specificity for a polypeptide having a sequence chosen from: SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 20 or fragments, analogues or derivatives thereof.
6. An isolated polynucleotide encoding a polypeptide capable of generating antibodies having binding specificity for a polypeptide having a sequence chosen from: SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16 or 20.
7. An isolated polynucleotide that is complementary to the polynucleotide of any of claims 1 to 6.
8. The polynucleotide of any of claims 1 to 6, wherein said polynucleotide is DNA.

9. The polynucleotide of any of claims 1 to 6, wherein said polynucleotide is RNA.
10. A polynucleotide which hybridizes under stringent conditions to a second polynucleotide having a sequence chosen from: SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 19.
11. A polynucleotide according to claim 10 wherein said polynucleotide has at least 95% complementarity to the second polynucleotide.
12. A polynucleotide which hybridizes under stringent conditions to a second polynucleotide having a sequence chosen from: SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 19.
13. A polynucleotide according to claim 12 wherein said polynucleotide has at least 95% complementarity to the second polynucleotide.
14. An isolated polynucleotide having a sequence comprising SEQ ID NO:19.
15. A vector comprising the polynucleotide of any of claims 1 to 6 or 10 to 14, wherein said DNA is operably linked to an expression control region.
16. A vector comprising the polynucleotide of claim 7, wherein said DNA is operably linked to an expression control region.
17. A host cell transfected with the vector of claim 15.
18. A host cell transfected with the vector of claim 16.

19. A process for producing a polypeptide comprising culturing a host cell according to claim 17 under conditions suitable for expression of said polypeptide.
20. A process for producing a polypeptide comprising culturing a host cell according to claim 18 under condition suitable for expression of said polypeptide.
21. An isolated polypeptide having at least 70% identity to a second polypeptide having an amino acid sequence chosen from: SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20 or fragments, analogues or derivatives thereof.
22. An isolated polypeptide having at least 95% identity to a second polypeptide having an amino acid sequence chosen from: SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20 or fragments, analogues or derivatives thereof.
23. An isolated polypeptide having at least 70% identity to a second polypeptide having an amino acid sequence chosen from: SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16 or 20.
24. An isolated polypeptide having at least 95% identity to a second polypeptide having an amino acid sequence chosen from: SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16 or 20.
25. An isolated polypeptide capable of generating antibodies having binding specificity for a second polypeptide having a sequence chosen from: SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20 or fragments, analogues or derivatives thereof.
26. An isolated polypeptide capable of generating antibodies having binding specificity for a second polypeptide having a sequence chosen from: SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16 or 20.



27. An isolated polypeptide having an amino acid sequence chosen from SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 20 or fragments, analogues or derivatives thereof.
28. An isolated polypeptide having an amino acid sequence chosen from SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16 or 20.
29. An isolated polypeptide according to any of claims 21 to 28, wherein the N-terminal Met residue is deleted.
30. An isolated polypeptide according to any of claims 21 to 28, wherein the secretory amino acid sequence is deleted.
31. An isolated polypeptide according to claim 29, wherein the secretory amino acid sequence is deleted.
32. A vaccine composition comprising a polypeptide according to any one of claims 21 to 28 and a pharmaceutically acceptable carrier, diluent or adjuvant.
33. A vaccine composition comprising a polypeptide according to claim 29 and a pharmaceutically acceptable carrier, diluent or adjuvant.
34. A vaccine composition comprising a polypeptide according to claim 30 and a pharmaceutically acceptable carrier, diluent or adjuvant.
35. A vaccine composition comprising a polypeptide according to claim 31 and a pharmaceutically acceptable carrier, diluent or adjuvant.
36. A method for therapeutic or prophylactic treatment of pharyngitis, erysipelas and impetigo, scarlet fever, and invasive diseases such as bacteremia and necrotizing fasciitis in an individual susceptible to pharyngitis,

erysipelas and impetigo, scarlet fever, and invasive diseases such as bacteremia and necrotizing fasciitis and also toxic shock comprising administering to said individual a therapeutic or prophylactic amount of a composition according to claim 32.

37. A method for therapeutic or prophylactic treatment of pharyngitis, erysipelas and impetigo, scarlet fever, and invasive diseases such as bacteremia and necrotizing fasciitis in an individual susceptible to pharyngitis, erysipelas and impetigo, scarlet fever, and invasive diseases such as bacteremia and necrotizing fasciitis and also toxic shock comprising administering to said individual a therapeutic or prophylactic amount of a composition according to claim 33.

38. A method for therapeutic or prophylactic treatment of pharyngitis, erysipelas and impetigo, scarlet fever, and invasive diseases such as bacteremia and necrotizing fasciitis in an individual susceptible to pharyngitis, erysipelas and impetigo, scarlet fever, and invasive diseases such as bacteremia and necrotizing fasciitis and also toxic shock comprising administering to said individual a therapeutic or prophylactic amount of a composition according to claim 34.

39. A method for therapeutic or prophylactic treatment of pharyngitis, erysipelas and impetigo, scarlet fever, and invasive diseases such as bacteremia and necrotizing fasciitis in an individual susceptible to pharyngitis, erysipelas and impetigo, scarlet fever, and invasive diseases such as bacteremia and necrotizing fasciitis and also toxic shock comprising administering to said individual a therapeutic or prophylactic amount of a composition according to claim 35.

40. A method for therapeutic or prophylactic treatment of Streptococcus pyogenes bacterial infection in an individual susceptible to Streptococcus pyogenes infection comprising administering to said individual a therapeutic or prophylactic amount of a composition according to claim 32.
41. A method for therapeutic or prophylactic treatment of Streptococcus pyogenes bacterial infection in an individual susceptible to Streptococcus pyogenes infection comprising administering to said individual a therapeutic or prophylactic amount of a composition according to claim 33.
42. A method for therapeutic or prophylactic treatment of Streptococcus pyogenes bacterial infection in an individual susceptible to Streptococcus pyogenes infection comprising administering to said individual a therapeutic or prophylactic amount of a composition according to claim 34.
43. A method for therapeutic or prophylactic treatment of Streptococcus pyogenes bacterial infection in an individual susceptible to Streptococcus pyogenes infection comprising administering to said individual a therapeutic or prophylactic amount of a composition according to claim 35.
44. Use of a vaccine composition according to claim 32 for the prophylactic or therapeutic treatment of Streptococcal infection in an individual susceptible to or infected with streptococcal infection comprising administering to said individual a prophylactic or therapeutic amount of the composition.
45. Use of a vaccine composition according to claim 33 for the prophylactic or therapeutic treatment of Streptococcal infection in an individual susceptible to or infected with streptococcal infection comprising administering to said

individual a prophylactic or therapeutic amount of the composition.

46. Use of a vaccine composition according to claim 34 for the prophylactic or therapeutic treatment of Streptococcal infection in an individual susceptible to or infected with streptococcal infection comprising administering to said individual a prophylactic or therapeutic amount of the composition.

47. Use of a vaccine composition according to claim 35 for the prophylactic or therapeutic treatment of Streptococcal infection in an individual susceptible to or infected with streptococcal infection comprising administering to said individual a prophylactic or therapeutic amount of the composition.

Figure 1

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1  ATGATTATTA  CTAAAAAGAG  CTTATT'TGTG  ACAAGTGTCTG  CTTTGTCTGTT  AGCACCTTTG
61  GCGACAGCAC  AGGCACAAGA  GTGGACACCA  CGATCGGTTA  CAGAAATCAA  GTCTGAACCT
121  GTCCTAGTTG  ATAATGTTTT  TACTTATACT  GTAAAATACG  GTGACACTTT  AAGCACAAAT
181  GCTGAAGCAA  TGGGAATTGA  TGTGCATGTC  TTAGGAGATA  TTAATCATAT  TGCTAATATT
241  GACTTAATTT  TTCCAGACAC  GATCCTAACA  GCCAACTACA  ACCAACACGG  TCAGGCAACG
301  ACTTTGACGG  TTCAAGCGCC  TGCTTCTAGT  CCAGCTAGCG  TTAGTCATGT  ACCTAGCAGT
361  GAGCCATTAC  CCCAAGCATC  TGCCACCTCT  CAATCGACTG  TTCCTATGGC  ACCATCTGCG
421  ACACCATCTG  ATGTCCCAAC  GACACCATTC  GCATCTGCAA  AGCCAGATAG  TTCTGTGACA
481  GCGTCATCTG  AGCTCACATC  GTCAACGAAT  GATGTTTCGA  CTGAGTTGTC  TAGCGAATCA
541  CAAAAGCAGC  CAGAAGTACC  ACAAGAAGCA  GTTCCAACTC  CTAAAGCAGC  TGAAACGACT
601  GAAGTCGAAC  CTAAGACAGA  CATCTCAGAG  GATTCAACTT  CAGCTAATAG  GCCTGTACCT
661  AACGAGAGTG  CTTCAGAAGA  AGTTTCTTCT  GCGGCCCCAG  CACAAGCCCC  AGCAGAAAAA
721  GAAGAAACCT  CTGCGCCAGC  AGCACAAAAA  GCTGTAGCTG  ACACCACAAG  TGTGCAACC
781  TCAAATGGCC  TTTCTTACGC  TCCAAACCAT  GCCTACAATC  CAATGAATGC  AGGGCTTCAA
841  CCACAAACAG  CAGCCTTCAA  AGAAGAAGTG  GCTTCTGCCT  TTGGTATTAC  GTCATTTAGT
901  GGTTACCGTC  CAGGTGATCC  AGGAGATCAT  GGTAAAGGTT  TGGCCATTGA  TTTTATGGTG
961  CCTGAAAATT  CTGCTCTTGG  TGATCAAGTT  GCTCAATATG  CCATTGACCA  TATGGCAGAG
1021  CGTGGTATTT  CATACGTTAT  TTGGAAACAG  CGATICTATG  CGCCATTTCG  AAGTATTTAC
1081  GGACCAGCCT  ACACATGGAA  CCCCATGCCA  GATCGCGGCA  GTATTACAGA  AAACCATTAT
1141  GATCATGTTT  ATGTCTCCTT  TAATGCTTAA (SEQ ID NO:1)

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Figure 2

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1  MIITKKSFLV  TSVALSLAPL  ATAQAQWTP  RSVTEIKSEL  VLVDNVFTYT  VKYGDTLSTI
61  AEAMGIDVHV  LGDINHIANI  DLIFPDILT  ANYNQHQAT  TLTVQAPASS  PASVSHVPSS
121  EPLPQASATS  QSTVPMAPSA  TPSDVPTTF  ASAKPDSSVT  ASSELTSSSTN  DVSTELSSSES
181  QKQPEVPQEA  VPTPKAAETT  EVEPKTDISE  DSTSANRPVP  NESASEEVSS  AAPAQAPAEK
241  EETSAPAAQK  AVADTTSVAT  SNGLSYAPNH  AYNPMNAGLQ  PQTAAPKEEV  ASAFGITSFS
301  GYRPGDPGDH  GKGLAIDFMV  PENSALGDQV  AQYAIHMAE  RGISYVIWKQ  RFYAPFASIY
361  GPAYTWNPM  DRGSITENHY  DHVHVSFNA* (SEQ ID NO:2)

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Figure 3

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1  ATGATTATTA CTAAAAAGAG CTTATTTGTG ACAAGTGTG CTTTGTGCGT AGCACCTTTG
61  GCGACAGCGC AGGCACAAGA GTGGACACCA CGATCGGTTA CAGAAATCAA GTCTGAACTC
121 GTCCTAGTTG ATAATGTTTT TACTTATATA GTAAAATACG GTGACACTTT AAGCACAAAT
181 GCTGAAGCAA TGGGGATTGA TGTGCATGTC TTAGGAGATA TTAATCATAT TGCTAATATT
241 GACTTAATTT TTCCAGACAC GATCCTAACA GCAAACTACA ACCAACACGG TCAGGCAACG
301 ACTTTGACGG TTCAAGCACC TGCTTCTAGT CCATCTAGCG TTAGTCATGT ACCTAGCAGT
361 GAGCCATTAC CCCAAGCATC TGCCACCTCT CAACCGACTG TTCCTATGGC ACCATCTGCG
421 ACACCATCTG ATGTCCCAAC GACACCATTG GCATCTGCAA AGCCAGATAG TTCTGTGACA
481 GCGTCATCTG AGCTCACATC GTCAACGAAT GATGTTTCGA CTGAGTTGTC TAGCGAATCA
541 CAAAAGCAGC CAGAAGTACC ACAAGAAGCA GTTCCTAACTC CTAAAGCAGC TGAACCGACT
601 GAAGTCGAAC CTAAGACAGA CATCTCAGAA GACCCAACTT CAGCTAATAG GCCTGTACCT
661 AACGAGAGTG CTTCAGAAGA AGCTTCTTCT GCGGCCCCAG CACAAGCTCC AGCAGAAAAA
721 GAAGAAACCT CTCAGATGTT AACTGCGCCA GCAGCACAAA AAGCTGTAGC TGACACCACA
781 AGTGTGCAA CCTCAAACGG CCTTTCTTAC GCTCCAAACC ATGCCTACAA TCCAATGAAT
841 GCAGGGCTTC AACCACAAAC AGCAGCCTTC AAAGAAGAAG TGGCTTCTGC CTTTGGTATT
901 ACGTCATTTA GTGGTTACCG TCCAGGAGAT CCAGGAGATC ATGGTAAAGG ATTAGCCATT
961 GACTTTATGG TACCGGTTAG CTCTACGCTT GGTGATCAAG TTGCTCAATA TGCCATTGAC
1021 CATATGGCAG AGCGTGGTAT TTCATACGTT ATTTGGAAAC AGCGATTCTA TCGGCCATTT
1081 GCAAGTATTT ACGGACCAGC CTACACATGG AACCCCATGC CAGATCGCGG CAGTATTACA
1141 GAAAACCATT ATGATCATGT TCATGTCTCC TTTAATGCTT AA (SEQ ID NO:3)

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Figure 4

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1  MIITKKSFLV TSVALSLAPL ATAQAQWTP RSVTEIKSEL VLVDNVFTYI VKYGDTLSTI
61  AEAMGIDVHV LGDINHIANI DLIFPDILT ANYNQHGQAT TLTVQAPASS PSSVSHVPSS
121 EPLPQASATS OPTVPMAPSA TPSDVPTTTF ASAKPDSSVT ASSELTSTSN DVSTELSSSES
181 QKQPEVPQEA VPTPKAABPT EVEPKTDISE DPTSANRPVP NESASEEASS AAPAQAPAEK
241 EETSQMLTAP AAQKAVADTT SVATSNGLSY APNHAYNPMN AGLQPQTAAF KEEVASAFGI
301 TSFSGYRPGD PGDEHGKLAI DFMVPSSTL GDQVAQYAIH HMAERGISYV IWKQRFYAPF
361 ASIYGPAITW NPMPDRGSIT ENHYDHVHVS FNA* (SEQ ID NO:4)

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Figure 5

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1  ATGATTATTA CTAAAAAGAG CTTATTTGTG ACAAGTGTCTG CTTTGTCGTT AGTACCTTTG
61  GCGACAGCGC AGGCACAAGA GTGGACACCA CGATCGGTTA CAGAAATCAA GTCTGAACCTC
121 GTCCTAGTTG ATAATGTTTT TACTTTATACT GTAAAATACG GTGACACTTT AAGCACAATT
181 GCTGAAGCAA TGGGGATTGA TGTGCAATGTC TTAGGAGATA TTAATCATAT TGCTAATATT
241 GACCTAATTT TTCCAGACAC GATCCTAACA GCAAACTACA ATCAACACGG TCAGGCAACG
301 AATTTGACGG TTCAAGCACC TGCTTCTAGT CCAGCTAGCG TTAGTCATGT ACCTAGCAGT
361 GAGCCATTAC CCCAAGCATC TGCCACCTCT CAACCGACTG TTCCTATGGC ACCACCTGCG
421 ACACCATCTG ATGTCCCAAC GACACCATTC GCATCTGCAA AGCCAGATAG TTCTGTGACA
481 GCGTCATCTG AGCTCACATC GTCAACGAAT GATGTTTCGA CTGAGTTGTC TAGCGAATCA
541 CAAAAGCAGC CAGAAGTACC ACAAGAAGCA GTTCCAATC CTAAAGCAGC TGAAACGACT
601 GAAGTCGAAC CTAAGACAGA CATCTCAGAA GCCCCAATT CAGCTAATAG GCCTGTACCT
661 AACGAGAGTG CTTCAGAAGA AGTTTCTTCT GCGGCCCCAG CACAAGCCCC AGCAGAAAAA
721 GAAGAAACCT CTGCGCCAGC AGCACAAAAA GCTGTAGCTG ACACCACAAG TGTGCAAC
781 TCAATGGCC TTTCTTACGC TCCAAACCAT GCCTACAATC CAATGAATGC AGGGCTTCAA
841 CCACAAACAG CAGCCTTCAA AGAAGAAGTG GCTTCTGCCT TTGGTATTAC GTCATTTAGT
901 GGTTACCGTC CAGGTGATCC AGGAGATCAT GGTAAAGGTT TGGCCATTGA TTTTATGCTG
961 CCTGAAAATT CTGCTCTTGG TGATCAAGTT GCTCAATATG CCATTGACCA TATGGCAGAG
1021 CGTGGTATTT CATACGTTAT TTGGAAACAG CGATTCTATG CGCCATTGTC AAGTATTTAC
1081 GGACCAGCCT ACACATGGAA CCCCATGCCA GATCGCGGCA GTATTACAGA AAACCATTTAT
1141 GATCATGTTT ATGTCTCCTT TAATGCTTAA (SEQ ID NO:5)

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Figure 6

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1  MIITKKSLEFV TSVALSLVPL ATAQAQEWTP RSVTEIKSEL VLVDNVFTYT VKYGDTLSTI
61  AEAMGIDVHV LGDINHIANI DLIFPDITLT ANYNQHQQAT NLTVQAPASS PASVSHVPSS
121 EPLPQASATS QPTVPMAPPA TPSDVPTTTF ASAKPDSSVT ASSELTSSSTN DVSTELSSSES
181 QKQPEVPQEA VTPKAAETT EVEPKTDISE APTSANRPVP NESASEEVSS AAPAQAPAEK
241 EETSAPAAQK AVADTTSVAT SNGLSYAPNH AYNPMNAGLQ PQTAAFKEEV ASAFGITSFS
301 GYRPGDPPDH GKGLAIDFMV PENSALGDQV AQYAIHMAE RGISYVIWKQ RFYAPFASIY
361 GPAYTWNPMMP DRGSITENHY DHVHVSFNA* (SEQ ID NO:6)

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Figure 7

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1  ATGATTATTA CTAAAAAGAG CTTATTGTG ACAAGTGTG CTTTGTGTT AGCACCTTTG
61  GCGACAGCGC AGGCACAAGA GTGGACACCA CGATCGGTTA CAGAAATCAA GTCTGAACTC
121 GTCCTAGTTG ATAATGTTTT TACTTATACA GTAAAATACG GTGACACTTT AAGCACAATT
181 GCTGAAGCAA TGGGGATTGA TGTGCATGTC TTAGGAGATA TTAATCATAT TGCTAATATT
241 GACTTAATTT TTCCAGACAC GATCCTAACA GCAAACACG ATCAACACGG TCAGGCAACG
301 ACTTTGACGG TTCAAGCACC TGCTTCTAGT CCAGCTAGCG TTAGTCATGT ACCTAGCAGT
361 GAGCCATTAC CCCAAGCATC TGCCACCTCT CAACCGACTG TTCCTATGGC ACCATCTGCG
421 ACACCATTAG CATCTGCAAA GCCAGATAGT TCTGTGACAG CGTCATCTGA GCTCACATCG
481 TCAACGAATG ATGTTTCGAC TGAGTCGTCT AGCGAATCAC AAAAGCAGCC AGAAGTACCA
541 CAAGAAGCAG TTCCAACCTC TAAAGCAGCT GAAACGACTG AAGTCGAACC TAAGACAGAC
601 ATCTCAGAAG ACCCAACTTC AGCTAATAGG CCTGTACCTA ACGAGAGTGC TTCAGAAGAA
661 GTTCTTCTCG CGGCCCCAGC ACAAGCCCCA GCAGAAAAAG AAGAAACCTC TGCGCCAGCA
721 GCACAAAAAG CTGTAGCTGA CACCACAAGT GTTGCAACCT CAAACGGCCT TTCTTACGCT
781 CCAAACCATG CCTACAATCC AATGAATGCA GGGCTTCAAC CACAAACAGC AGCCTTCAAA
841 GAAGAAGTGG CTTCTGCCCT TGGTATTACG TCATTTAGTG GTTACCGTCC AGGTGACCCA
901 GGAGATCATG GTAAAGGTTT GGCCATTGAT TTTATGGTGC CTGAAAATTC TGCTCTTGTT
961 GATCAAGTTG CTCAATATGC CATTGACCAT ATGGCAGAGC GTGGTATTTT ATACGTTATT
1021 TGGAAACAGC GATTCTATGC GCCATTGCA AGTATTTACG GACCAGCTTA CACATGGAAC
1081 CCCATGCCAG ATCGCGGCAG TATTACAGAA AACCATTATG ATCATGTTCA TGTCTCCTTT
1141 AATGCTTAA (SEQ ID NO:7)

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Figure 8

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1  MIITKKSLEF TSVALSLAPL ATAQAQEWTP RSVTEIKSEL VLVDNVFTYT VKYGDTLSTI
61  AEAMGIDVHV LGDINHIANI DLIFPDILT ANYNQHQAT TLTVQAPASS PASVSHVPSS
121 EPLPQASATS QPTVPMAPSA TPLASAKPDS SVTASSELTS STNDVSTESS SESQKQPEVP
181 QEAVPTPKAA ETTEVEPKTD ISEDPTSANR PVPNESASBE VSSAAPAQAP AEKBETSAPA
241 AQKAVADTTS VATSNGLSYA PNHAYNPMNA GLQPQTAAFK EEVASAFGIT SPSGYRPGDP
301 GDHGKGLAID FMVPENSALG DQVAQYAIH MAERGISYVI WKQRFYAPFA SIYGPAYTWN
361 PMPDRGSITE NHYDHVHVSF NA* (SEQ ID NO:8)

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Figure 9

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1   CAAGAGTGGA CACCACGATC GGTACAGAA ATCAAGTCTG AACTCGTCCT AGTTGATAAT
61  GTTTTTACTT ATACTGTAAA ATACGGTGAC ACTTTAAGCA CAATTGCTGA AGCAATGGGA
121 ATTGATGTGC ATGTCTTAGG AGATATTAAT CATATTGCTA ATATTGACTT AATTTTTCCA
181 GACACGATCC TAACAGCCAA CTACAACCAA CACGGTCAGG CAACGACTTT GACGGTTCAA
241 GCGCCTGCTT CTAGTCCAGC TAGCGTTAGT CATGTACCTA GCAGTGAGCC ATTACCCCAA
301 GCATCTGCCA CCTCTCAATC GACTGTTCTT ATGGCACCAT CTGCGACACC ATCTGATGTC
361 CCAACGACAC CATTGCGATC TGCAAAGCCA GATAGTTCTG TGACAGCGTC ATCTGAGCTC
421 ACATCGTCAA CGAATGATGT TTCGACTGAG TTGTCTAGCG AATCACAAAA GCAGCCAGAA
481 GTACCACAAG AAGCAGTTCC AACTCCTAAA GCAGCTGAAA CGACTGAAGT CGAACCTAAG
541 ACAGACAICT CAGAGGATTC AACTTCAGCT AATAGGCCTG TACCTAACGA GAGTGCTTCA
601 GAAGAAGTTT CTTCTGCGGC CCCAGCACAA GCCCCAGCAG AAAAAGAAGA AACCTCTGCG
661 CCAGCAGCAC AAAAAGCTGT AGCTGACACC ACAAGTGTG CAACCTCAA TGGCCTTTCT
721 TACGCTCCAA ACCATGCCTA CAATCCAATG AATGCAGGGC TTCAACCACA AACAGCAGCC
781 TTCAAAGAAG AAGTGGCTTC TGCCTTTGGT ATTACGTCAT TTAGTGGTTA CCGTCCAGGT
841 GATCCAGGAG ATCATGGTAA AGGTTTGGCC ATTGATTTTA TGGTGCCTGA AAATCTGCT
901 CTTGGTGATC AAGTTGCTCA ATATGCCATT GACCATATGG CAGAGCGTGG TATTTCATAC
961 GTTATTTGGA AACAGCGATT CTATGCGCCA TTTGCAAGTA TTTACGGACC AGCCTACACA
1021 TGGAACCCCA TGCCAGATCG CGGCAGTATT ACAGAAAACC ATTATGATCA TGTCATGTC
1081 TCCTTTAATG CTAA (SEQ ID NO:9)

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Figure 10

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1   QEWTPRSVTE IKSELVLVDN VFTYTVKYGD TLSTIAEAMG IDVHVLGDIN HIANIDLIFP
61  DTILTANYNQ HGQATTLTVQ APASSPASVS HVPSSSEPLPQ ASATSQSTVP MAPSATPSDV
121 PTPPFASAKP DSSVTASSEL TSSTNDVSTE LSSESQKQPE VPQEA VPTPK AAETTEVEPK
181 TDISEDSTSA NRPVPNESAS EEVSSAAPAQ APAEKEETSA PAAQKAVADT TSVATSNGLS
241 YAPNHAYNPM NAGLQPQTAA FKEEVASAFG ITSFSGYRPG DPGDHGKGLA IDFMVPENSA
301 LGDQVAQYAI DHMAERGISEY VIWKQRFYAP FASIYGPAYT WNPMPDRGSI TENHYDHSVH
361 SFNA* (SEQ ID NO:10)

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Figure 11

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1   CAAGAGTGGA CACCACGATC GGTACAGAA ATCAAGTCTG AACTCGTCCT AGTTGATAAT
61  GTTTTACTT ATATAGTAAA ATACGGTGAC ACTTTAAGCA CAATTGCTGA AGCAATGGGG
121 ATTGATGTGC ATGTCTTAGG AGATATTAAT CATATTGCTA ATATTGACTT AATTTTTCCA
181 GACACGATCC TAACAGCAAA CTACAACCAA CACGGTCAGG CAACGACTTT GACGGTTCAA
241 GCACCTGCTT CTAGTCCATC TAGCGTTAGT CATGTACCTA GCAGTGAGCC ATTACCCCAA
301 GCATCTGCCA CCTCTCAACC GACTGTTCTT ATGGCACCAT CTGCGACACC ATCTGATGTC
361 CCAACGACAC CATTCGCATC TGCAAAGCCA GATAGTTCTG TGACAGCGTC ATCTGAGCTC
421 ACATCGTCAA CGAATGATGT TTCGACTGAG TTGTCTAGCG AATCACAAAA GCAGCCAGAA
481 GTACCACAAG AAGCAGTTCC AACTCCTAAA GCAGCTGAAC CGACTGAAGT CGAACCTAAG
541 ACAGACATCT CAGAAGACCC AACTTCAGCT AATAGGCCTG ACCTAACGA GAGTGCTTCA
601 GAAGAAGCTT CTTCTGCGGC CCCAGCACAA GCTCCAGCAG AAAAAGAAGA AACCTCTCAG
661 ATGTTAACTG CGCCAGCAGC ACAAAAAGCT GTAGCTGACA CCACAAGTGT TGCAACCTCA
721 AACGGCCTTT CTTACGCTCC AAACCATGCC TACAATCCAA TGAATGCAGG GCTTCAACCA
781 CAAACAGCAG CCTTCAAAGA AGAAGTGGCT TCTGCCTTTG GTATTACGTC ATTTAGTGGT
841 TACCGTCCAG GAGATCCAGG AGATCATGGT AAAGGATTAG CCATTGACTT TATGGTACCG
901 GTTAGCTCTA CGCTTGGTGA TCAAGTTGCT CAATATGCCA TTGACCATAT GGCAGAGCGT
961 GGTATTTTCA ACGTTATTTG GAAACAGCGA TTCTATGCGC CATTTGCAAG TATTTACGGA
1021 CCAGCCTACA CATGGAACCC CATGCCAGAT CGCGGCAGTA TTACAGAAAA CCATTATGAT
1081 CATGTTTCATG TCTCCTTTAA TGCTTAA (SEQ ID NO:11)

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Figure 12

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1   QEWTPRSVTE IKSELVLVDN VFTYIVKYGD TLSTIAEAMG IDVHVLGDIN HIANIDLIFP
61  DTILTANYNQ HGQATTLTVQ APASSPSSVS HVPSSSEPLPQ ASATSQPTVP MAPSATPSDV
121 PTTPFASAKP DSSVTASSEL TSSTNDVSTE LSSESQKQPE VPQEAVPTPK AAEPTVEVEPK
181 TDISEDPTSA NRPVPNESAS EEASSAAPAQ APAEKEETSQ MLTAPAAQKA VADTTSVATS
241 NGLSYAPNHA YNPMNAGLQP QTAAFKEEVA SAFGITSFSG YRPGDPGDHG KGLAIDFMVP
301 VSSTLGDQVA QYAIIDHMAER GISYVIWKQR FYAPFASIYG PAYTWNMPMD RGSITENHYD
361 HVHVSFNA* (SEQ ID NO:12)

```

Figure 13

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1   CAAGAGTGGA CACCACGATC GGTACAGAA ATCAAGTCTG AACTCGTCCT AGTTGATAAT
61  GTTTTACTT ATACTGTAAA ATACGGTGAC ACTTTAAGCA CAATTGCTGA AGCAATGGGG
121 ATTGATGTGC ATGTCTTAGG AGATATTAAT CATATTGCTA ATATTGACCT AATTTTTCCA
181 GACACGATCC TAACAGCAAA CTACAATCAA CACGGTCAGG CAACGAATTT GACGGTTCAA
241 GCACCTGCTT CTAGTCCAGC TAGCGTTAGT CATGTACCTA GCAGTGAGCC ATTACCCCAA
301 GCATCTGCCA CCTCTCAACC GACTGTTCCCT ATGGCACCAC CTGCGACACC ATCTGATGTC
361 CCAACGACAC CATTCGCATC TGCAAAGCCA GATAGTTCTG TGACAGCGTC ATCTGAGCTC
421 ACATCGTCAA CGAATGATGT TTCGACTGAG TTGTCTAGCG AATCACAAAA GCAGCCAGAA
481 GTACCACAAG AAGCAGTTCC AACTCCTAAA GCAGCTGAAA CGACTGAAGT CGAACCTAAG
541 ACAGACATCT CAGAAGCCCC AACTTCAGCT AATAGGCCTG TACCTAACGA GAGTGCTTCA
601 GAAGAAGTTT CTCTGCGGC CCCAGCACAA GCCCCAGCAG AAAAAGAAGA AACCTCTGCG
661 CCAGCAGCAC AAAAAGCTGT AGCTGACACC ACAAGTGTG CAACCTCAA TGGCCTTTC
721 TACGTCCAA ACCATGCCTA CAATCCAATG AATGCAGGGC TTCAACCACA AACAGCAGCC
781 TTCAAAGAAG AAGTGGCTTC TGCTTTGGT ATTACGTCAT TTAGTGGTTA CCGTCCAGGT
841 GATCCAGGAG ATCATGGTAA AGGTTTGGCC ATTGATTTTA TGGTGCCTGA AAATTCGTCT
901 CTGCGTGATC AAGTTGCTCA ATATGCCATT GACCATATGG CAGAGCGTGG TATTTCATAC
961 GTTATTGGA AACAGCGATT CTATGCGCCA TTGCAAGTA TTTACGGACC AGCCTACACA
1021 TGGAACCCCA TGCCAGATCG CGGCAGTATT ACAGAAAACC ATTATGATCA TGTTCATGTC
1081 TCCTTTAATG CTTAA (SEQ ID NO:13)

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Figure 14

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1   QEWTPRSVE IKSELVLVDN VFTYTVKYGD TLSTIAEAMG IDVHVLGDIN HIANIDLIFP
61  DTILTANYNQ HGQATNLTVQ APASSPASVS HVPSSSEPLPQ ASATSQPTVP MAPPATPSDV
121 PTPPFASAKP DSSVTASSEL TSSTNDVSTE LSSESQKQPE VPQEA VPTPK AAETTEVEPK
181 TDISEAP TSA NRVPNESAS EEVSSAAPAQ APAEKEETSA PAAQKAVADT TSVATSNGLS
241 YAPNHAYNPM NAGLQPQTAA FKEEVASAFG ITSFSGYRPG DPGDHGKGLA IDFMVPENSA
301 LGDQVAQYAI DHMAERGISEY VIWKQRFYAP FASIYGPAYT WNPMPDRGSI TENHYDHVHV
361 SFNA* (SEQ ID NO:14)

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Figure 15

```

1   CAAGAGTGGA CACCACGATC GGTACAGAA ATCAAGTCTG AACTCGTCCT AGTTGATAAT
61  GTTTTACTT ATACAGTAAA ATACGGTGAC ACTTTAAGCA CAATTGCTGA AGCAATGGGG
121 ATTGATGTGC ATGTCTTAGG AGATATTAAT CATATTGCTA ATATTGACTT AATTTTCCCA
181 GACACGATCC TAACAGCAAA CTACAATCAA CACGGTCAGG CAACGACTTT GACGGTTCAA
241 GCACCTGCTT CTAGTCCAGC TAGCGTTAGT CATGTACCTA GCAGTGAGCC ATTACCCCAA
301 GCATCTGCCA CCTCTCAACC GACTGTTTCT ATGGCACCAT CTGCGACACC ATTAGCATCT
361 GCAAAGCCAG ATAGTTCTGT GACAGCGTCA TCTGAGCTCA CATCGTCAAC GAATGATGTT
421 TCGACTGAGT CGTCTAGCGA ATCACAAAAG CAGCCAGAAG TACCACAAGA AGCAGTTCCA
481 ACTCCTAAAG CAGCTGAAAC GACTGAAGTC GAACCTAAGA CAGACATCTC AGAAGACCCA
541 ACTTCAGCTA ATAGGCCTGT ACCTAACGAG AGTGCTTCAG AAGAAGTTTC TTCTGCGGCC
601 CCAGCACAAG CCCAGCAGA AAAAGAAGAA ACCTCTGCGC CAGCAGCACA AAAAGCTGTA
661 GCTGACACCA CAAGTGTTGC AACCTCAAAC GGCCTTTCTT ACGCTCCAAA CCATGCCTAC
721 AATCCAATGA ATGCAGGGCT TCAACCACAA ACAGCAGCCT TCAAAGAAGA AGTGGCTTCT
781 GCCTTTGGTA TTACGTCATT TAGTGTTTAC CGTCCAGGTG ACCCAGGAGA TCATGGTAAA
841 GGTTCGCCA TTGATTTTAT GGTGCCTGAA AATTCTGCTC TTGGTGATCA AGTTGCTCAA
901 TATGCCATTG ACCATATGGC AGAGCGTGGT ATTTCATACG TTATTTGGAA ACAGCGATTC
961 TATGCGCCAT TTGCAAGTAT TTACGGACCA GCTTACACAT GGAACCCCAT GCCAGATCGC
1021 GGCAGTATTA CAGAAAACCA TTATGATCAT GTTCATGTCT CCTTTAATGC TTAA (SEQ ID
NO:15)

```

Figure 16

```

1   QEWTPRSVTE IKSELVLVDN VFTYTVKYGD TLSTIAEAMG IDVHVLGDIN HIANIDLIFP
61  DTILTANYNQ HGQATTLTVQ APASSPASVS HVPSSSEPLPQ ASATSQPTVP MAPSATPLAS
121 AKPDSSVTAS SELTSSTNDV STESSSESQK QPEVPQEA VP TPKAAETTEV EPKTDISED
181 TSANRPVPNE SASEEVSSAA PAQAPAEKEE TSAPAAQKAV ADTTSVATSN GLSYAPNHAY
241 NPMNAGLQPQ TAAFKEEVAS AFGITSFSGY RPDGPDHGK GLAIDFMVPE NSALGDQVAQ
301 YAIDHMAERG ISYVIWKQRF YAPFASIYGP AYTWNMPDR GSITENHYDH VHSVFNAA*
(SEQ ID NO:16)

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Figure 17

12384	1	ATGATTATTACTAAAAAGAGCTTATTTGTGACAAGTGTTCGCTTTGTCGTT	50
2699	1	ATGATTATTACTAAAAAGAGCTTATTTGTGACAAGTGTTCGCTTTGTCGTT	50
B514	1	ATGATTATTACTAAAAAGAGCTTATTTGTGACAAGTGTTCGCTTTGTCGTT	50
Spy57	1	ATGATTATTACTAAAAAGAGCTTATTTGTGACAAGTGTTCGCTTTGTCGTT	50
U09352	1	ATGATTATTACTAAAAAGAGCTTATTTGTGACAAGTGTTCGCTTTGTCGTT	50
Oklahoma	1	ATGATTATTACTAAAAAGAGCTTATTTGTGACAAGTGTTCGCTTTGTCGTT	50
		*****	
12384	51	AGCACCTTTGGCGACAGCACAGGCACAAGAGTGGACACCACGATCGGTTA	100
2699	51	AGCACCTTTGGCGACAGCGCAGGCACAAGAGTGGACACCACGATCGGTTA	100
B514	51	AGCACCTTTGGCGACAGCGCAGGCACAAGAGTGGACACCACGATCGGTTA	100
Spy57	51	AGTACCTTTGGCGACAGCGCAGGCACAAGAGTGGACACCACGATCGGTTA	100
U09352	51	AGCACCTTTGGCGACAGCGCAGGCACAAGAGTGGACACCACGATCGGTTA	100
Oklahoma	51	AGTACCTTTGGCGACAGCGCAGGCACAAGAGTGGACACCACGATCGGTTA	100
		** *****	
12384	101	CAGAAATCAAGTCTGAACTCGTCCTAGTTGATAATGTTTTACTTATACT	150
2699	101	CAGAAATCAAGTCTGAACTCGTCCTAGTTGATAATGTTTTACTTATATA	150
B514	101	CAGAAATCAAGTCTGAACTCGTCCTAGTTGATAATGTTTTACTTATACA	150
Spy57	101	CAGAAATCAAGTCTGAACTCGTCCTAGTTGATAATGTTTTACTTATACT	150
U09352	101	CACAAATCAAGTCTGAACTCGTCCTAGTTGATAATGTTTTACTTATACA	150
Oklahoma	101	CAGAAATCAAGTCTGAACTCGTCCTAGTTGATAATGTTTTACTTATACT	150
		** *****	
12384	151	GTAAATACGGTGACACTTTAAGCACAATTGCTGAAGCAATGGGAATTGA	200
2699	151	GTAAATACGGTGACACTTTAAGCACAATTGCTGAAGCAATGGGGATTGA	200
B514	151	GTAAATACGGTGACACTTTAAGCACAATTGCTGAAGCAATGGGGATTGA	200
Spy57	151	GTAAATACGGTGACACTTTAAGCACAATTGCTGAAGCAATGGGGATTGA	200
U09352	151	GTAAATACGGTGACACTTTAAGCACAATTGCTGAAGCAATGGGGATTGA	200
Oklahoma	151	GTAAATACGGTGACACTTTAAGCACAATTGCTGAAGCAATGGGGATTGA	200
		*****	
12384	201	TGTGCATGTCTTAGGAGATATTAATCATATTGCTAATATTGACTTAATTT	250
2699	201	TGTGCATGTCTTAGGAGATATTAATCATATTGCTAATATTGACTTAATTT	250
B514	201	TGTGCATGTCTTAGGAGATATTAATCATATTGCTAATATTGACTTAATTT	250
Spy57	201	TGTGCATGTCTTAGGAGATATTAATCATATTGCTAATATTGACTTAATTT	250
U09352	201	TGTGCATGTCTTAGGAGATATTAATCATATTGCTAATATTGACTTAATTT	250
Oklahoma	201	TGTGCATGTCTTAGGAGATATTAATCATATTGCTAATATTGACTTAATTT	250
		*****	
12384	251	TTCCAGACACGATCCTAACAGCAAACCTACAACCAACACGGTCAGGCAACG	300
2699	251	TTCCAGACACGATCCTAACAGCAAACCTACAACCAACACGGTCAGGCAACG	300
B514	251	TTCCAGACACGATCCTAACAGCAAACCTACAATCAACACGGTCAGGCAACG	300
Spy57	251	TTCCAGACACGATCCTAACAGCAAACCTACAATCAACACGGTCAGGCAACG	300
U09352	251	TTCCAGACACGATCCTAACAGCAAACCTACAACCAACACGGTCAGGCAACG	300
Oklahoma	251	TTCCAGACACGATCCTAACAGCAAACCTACAATCAACACGGTCAGGCAACG	300
		*****	
12384	301	ACTTTGACGGTTCAAGCGCCTGCTTCTAGTCCAGCTAGCGTTAGTCATGT	350
2699	301	ACTTTGACGGTTCAAGCACCTGCTTCTAGTCCATCTAGCGTTAGTCATGT	350
B514	301	ACTTTGACGGTTCAAGCACCTGCTTCTAGTCCAGCTAGCGTTAGTCATGT	350
Spy57	301	AATTTGACGGTTCAAGCACCTGCTTCTAGTCCAGCTAGCGTTAGTCATGT	350
U09352	301	ACTTTGACGGTTCAAGCGCCTGCTTCTAGTCCAGCTAGCGTTAGTCATGT	350
Oklahoma	301	AATTTGACGGTTCAAGCACCTGCTTCTAGTCCAGCTAGCGTTAGTCATGT	350
		* *****	

```

12384      351 ACCTAGCAGTGAGCCATTACCCCAAGCATCTGCCACCTCTCAATCGACTG 400
2699      351 ACCTAGCAGTGAGCCATTACCCCAAGCATCTGCCACCTCTCAACCGACTG 400
B514      351 ACCTAGCAGTGAGCCATTACCCCAAGCATCTGCCACCTCTCAACCGACTG 400
Spy57     351 ACCTAGCAGTGAGCCATTACCCCAAGCATCTGCCACCTCTCAATCGACTA 400
U09352    351 ACCTAGCAGTGAGCCATTACCCCAAGCATCTGCCACCTCTCAACCGACTG 400
Oklahoma  351 ACCTAGCAGTGAGCCATTACCCCAAGCATCTGCCACCTCTCAACCGACTG 400
          *****

12384      401 TTCCATATGGCACCATCTGCGACACCATCTGATGTCCCAACGACACCATTTC 450
2699      401 TTCCATATGGCACCATCTGCGACACCATCTGATGTCCCAACGACACCATTTC 450
B514      401 TTCCATATGGCACCATCTGCGACACCAT-----TA 429
Spy57     401 TTCCATATGGCACCACCTGCGACACCATCTGATGTCCCAACGACACCATTTC 450
U09352    401 TTCCATATGGCACCATCTGCGACACCATCTGATGTCCCAACGACACCATTTC 450
Oklahoma  401 TTCCATATGGCACCACCTGCGACACCATCTGATGTCCCAACGACACCATTTC 450
          *****

12384      451 GCATCTGCAAAGCCAGATAGTTCTGTGACAGCGTCATCTGAGCTCACATC 500
2699      451 GCATCTGCAAAGCCAGATAGTTCTGTGACAGCGTCATCTGAGCTCACATC 500
B514      430 GCATCTGCAAAGCCAGATAGTTCTGTGACAGCGTCATCTGAGCTCACATC 479
Spy57     451 GCATCTGCAAAGCCAGATAGTTCTGTGACAGCGTCATCTGAGCTCACATC 500
U09352    451 GCATCTGCAAAGCCAGATAGTTTGTGACAGCGTCATCTGAGCTCACATC 500
Oklahoma  451 GCATCTGCAAAGCCAGATAGTTCTGTGACAGCGTCATCTGAGCTCACATC 500
          *****

12384      501 GTCAACGAATGATGTTTCGACTGAGTTGTCTAGCGAATCACAAGCAGC 550
2699      501 GTCAACGAATGATGTTTCGACTGAGTTGTCTAGCGAATCACAAGCAGC 550
B514      480 GTCAACGAATGATGTTTCGACTGAGTCGTCTAGCGAATCACAAGCAGC 529
Spy57     501 GTCAACGAATGATGTTTCGACTGAGTTGTCTAGCGAATCACAAGCAGC 550
U09352    501 ATCAACGAATGATGTTTCGACTGAGTTGTCTAGCGAATCACAAGCAGC 550
Oklahoma  501 GTCAACGAATGATGTTTCGACTGAGTTGTCTAGCGAATCACAAGCAGC 550
          *****

12384      551 CAGAAGTACCACAAGAAGCAGTTCCAACCTCTAAAGCAGCTGAAACGACT 600
2699      551 CAGAAGTACCACAAGAAGCAGTTCCAACCTCTAAAGCAGCTGAAACGACT 600
B514      530 CAGAAGTACCACAAGAAGCAGTTCCAACCTCTAAAGCAGCTGAAACGACT 579
Spy57     551 CAGAAGTACCACAAGAAGCAGTTCCAACCTCTAAAGCAGCTGAAACGACT 600
U09352    551 CAGAAGTACCACAAGAAGCAGAACCAACTCTAAAGCAGCTGAAACGACT 600
Oklahoma  551 CAGAAGTACCACAAGAAGCAGTTCCAACCTCTAAAGCAGCTGAAACGACT 600
          *****

12384      601 GAAGTCGAACCTAAGACAGACATCTCAGAGGATTCAACTTCAGCTAATAG 650
2699      601 GAAGTCGAACCTAAGACAGACATCTCAGAGACCCAACTTCAGCTAATAG 650
B514      580 GAAGTCGAACCTAAGACAGACATCTCAGAGACCCAACTTCAGCTAATAG 629
Spy57     601 GAAGTCGAACCTAAGACAGACATCTCAGAGCCCCAACTTCAGCTAATAG 650
U09352    601 GAAGTCGAACCTAAGACAGACATCTCAGAGATTCAACTTCAGCTAATAG 650
Oklahoma  601 GAAGTCGAACCTAAGACAGACATCTCAGAGCCCCAACTTCAGCTAATAG 650
          *****

12384      651 GCCTGTACCTAACGAGAGTGCTTCAGAAGAAGTTTCTTCTGCGGCCCCAG 700
2699      651 GCCTGTACCTAACGAGAGTGCTTCAGAAGAAGTTTCTTCTGCGGCCCCAG 700
B514      630 GCCTGTACCTAACGAGAGTGCTTCAGAAGAAGTTTCTTCTGCGGCCCCAG 679
Spy57     651 GCCTGTACCTAACGAGAGTGCTTCAGAAGAAGTTTCTTCTGCGGCCCCAG 700
U09352    651 GCCTGTACCTAACGGAAGTGCTTCAGAAGAAGTTTCTTCTGCGGCCCCAG 700
Oklahoma  651 GCCTGTACCTAACGAGAGTGCTTCAGAAGAAGTTTCTTCTGCGGCCCCAG 700
          *****

12384      701 CACAAGCCCCAGCAGAAAAAGAAGAAACCTCT-----GCGCCA 738
2699      701 CACAAGCTCCAGCAGAAAAAGAAGAAACCTCTCAGATGTTAACTGCGCCA 750
B514      680 CACAAGCCCCAGCAGAAAAAGAAGAAACCTCT-----GCGCCA 717
Spy57     701 CACAAGCTCCAGCAGAAAAAGAAGAAACCTCT-----GCGCCA 738
U09352    701 CACAAGCTCCAGCAGAAAAAGAAGAAACCTCTCAGATGTTAACTGCGCCA 750
Oklahoma  701 CACAAGCCCCAGCAGAAAAAGAAGAAACCTCT-----GCGCCA 738
          *****

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12384	739	GCAGCACAAAAAGCTGTAGCTGACACCACAAGTGTGCAACCTCAAATGG	788
2699	751	GCAGCACAAAAAGCTGTAGCTGACACCACAAGTGTGCAACCTCAAACGG	800
B514	718	GCAGCACAAAAAGCTGTAGCTGACACCACAAGTGTGCAACCTCAAACGG	767
Spy57	739	GCAGCACAAAAAGCTGTAGCTGACACCACAAGTGTGCAACCTCAAATGG	788
U09352	751	GCAGCACAAAAAGCTGTAGCTGACACCACAAGTGTGCAACCTCAAACGG	800
Oklahoma	739	GCAGCACAAAAAGCTGTAGCTGACACCACAAGTGTGCAACCTCAAATGG	788
***** **			
12384	789	CCTTTCTTACGCTCCAAACCATGCCTACAATCCAATGAATGCAGGGCTTC	838
2699	801	CCTTTCTTACGCTCCAAACCATGCCTACAATCCAATGAATGCAGGGCTTC	850
B514	768	CCTTTCTTACGCTCCAAACCATGCCTACAATCCAATGAATGCAGGGCTTC	817
Spy57	789	CCTTTCTTACGCTCCAAACCATGCCTACAATCCAATGAATGCAGGGCTTC	838
U09352	801	CCTTTCTTACGCTCCAAACCATGCCTACAATCCAATGAATGCAGGGCTTC	850
Oklahoma	789	CCTTTCTTACGCTCCAAACCATGCCTACAATCCAATGAATGCAGGGCTTC	838
*****			
12384	839	AACCACAAACAGCAGCCTTCAAAGAAGAAGTGGCTTCTGCCTTTGGTATT	888
2699	851	AACCACAAACAGCAGCCTTCAAAGAAGAAGTGGCTTCTGCCTTTGGTATT	900
B514	818	AACCACAAACAGCAGCCTTCAAAGAAGAAGTGGCTTCTGCCTTTGGTATT	867
Spy57	839	AACCACAAACAGCAGCCTTCAAAGAAGAAGTGGCTTCTGCCTTTGGTATT	888
U09352	851	AACCACAAACAGCAGCCTTCAAAGAAGAAGTG-CTTCTGCCTTTGGTATT	899
Oklahoma	839	AACCACAAACAGCAGCCTTCAAAGAAGAAGTGGCTTCTGCCTTTGGTATT	888
*****			
12384	889	ACGTCATTTAGTGGTTACCGTCCAGGTGATCCAGGAGATCAT-GGTAAAG	937
2699	901	ACGTCATTTAGTGGTTACCGTCCAGGAGATCCAGGAGATCAT-GGTAAAG	949
B514	868	ACGTCATTTAGTGGTTACCGTCCAGGTGACCCAGGAGATCAT-GGTAAAG	916
Spy57	889	ACGTCATTTAGTGGTTACCGTCCAGGTGATCCAGGAGATCAT-GGTAAAG	937
U09352	900	ACGTCATTTAGTGGTTACCGTCCAGGAGATCCAGGAGATCATGGTAAAG	949
Oklahoma	889	ACGTCATTTAGTGGTTACCGTCCAGGTGATCCAGGAGATCAT-GGTAAAG	937
***** ** *****			
12384	938	GTTTGGCCATTGATTTTATGGTGCCTGAAAATTCTGCTCTTGGTGATCAA	987
2699	950	GATTAGCCATTGACTTTATGGTACCGTTAGCTCTACGCTTGGTGATCAA	999
B514	917	GTTTGGCCATTGATTTTATGGTGCCTGAAAATTCTGCTCTTGGTGATCAA	966
Spy57	938	GTTTGGCCATTGATTTTATGGTGCCTGAAAATTCTGCTCTTGGTGATCAA	987
U09352	950	GATTAGCCATTGACTTTATGGTACCGTTAGCTCTACGCTTGGTGATCAA	999
Oklahoma	938	GTTTGGCCATTGATTTTATGGTGCCTGAAAATTCTGCTCTTGGTGATCAA	987
* ** ***** ** * * ** *			
12384	988	GTTGCTCAATATGCCATTGACCATATGGCAGAGCGTGGTATTTCATACGT	1037
2699	1000	GTTGCTCAATATGCCATTGACCATATGGCAGAGCGTGGTATTTCATACGT	1049
B514	967	GTTGCTCAATATGCCATTGACCATATGGCAGAGCGTGGTATTTCATACGT	1016
Spy57	988	GTTGCTCAATATGCCATTGACCATATGGCAGAGCGTGGTATTTCATACGT	1037
U09352	1000	GTTGCTCAATATGCCATTGACCATATGGCAGAGCGTGGTATTTCATACGT	1049
Oklahoma	988	GTTGCTCAATATGCCATTGACCATATGGCAGAGCGTGGTATTTCATACGT	1037
*****			
12384	1038	TATTTGGAACAGCGATTCTATGCGCCATTTGCAAGTATTTACGGACCAG	1087
2699	1050	TATTTGGAACAGCGATTCTATGCGCCATTTGCAAGTATTTACGGACCAG	1099
B514	1017	TATTTGGAACAGCGATTCTATGCGCCATTTGCAAGTATTTACGGACCAG	1066
Spy57	1038	TATTTGGAACAGCGATTCTATGCGCCATTTGCAAGTATTTACGGACCAG	1087
U09352	1050	TATTTGGAACAGCGATTCTATGCGCCATTTGCAAGTATTTACGGACCAG	1099
Oklahoma	1038	TATTTGGAACAGCGATTCTATGCGCCATTTGCAAGTATTTACGGACCAG	1087
*****			

WO 02/04495

PCT/CA01/01001

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12384 1088 CCTACACATGGAACCCCATGCCAGATCGCGGCAGTATTACAGAAAACCAT 1137
2699 1100 CCTACACATGGAACCCCATGCCAGATCGCGGCAGTATTACAGAAAACCAT 1149
B514 1067 CTTACACATGGAACCCCATGCCAGATCGCGGCAGTATTACAGAAAACCAT 1116
Spy57 1088 CCTACACATGGAACCCCATGCCAGATCGCGGCAGTATTACAGAAAACCAT 1137
U09352 1100 CCTACACATGGAACCCCATGCCAGATCGCGGCAGTATTACAGTTTCCAT 1149
Oklahoma 1088 CCTACACATGGAACCCCATGCCAGATCGCGGCAGTATTACAGAAAACCAT 1137
* *****
```

```
12384 1138 TATGATCATGTTTCATGTCTCCTTTAATGCTTAA 1170
2699 1150 TATGATCATGTTTCATGTCTCCTTTAATGCTTAA 1182
B514 1117 TATGATCATGTTTCATGTCTCCTTTAATGCTTAA 1149
Spy57 1138 TATGATCATGTTTCATGTCTCCTTTAATGCTTAA 1170
U09352 1150 TATGATCATGTTTCATGTCTCCTTTAATGCTTAA 1182
Oklahoma 1138 TATGATCATGTTTCATGTCTCCTTTAATGCTTAA 1170
*****
```



Figure 18

```

12384      1 MIITKKSLFVTSVALSLAPLATAQAQEWTPRSVTEIKSELVLVDNVFTYT  50
2699      1 MIITKKSLFVTSVALSLAPLATAQAQEWTPRSVTEIKSELVLVDNVFTYT  50
B514      1 MIITKKSLFVTSVALSLAPLATAQAQEWTPRSVTEIKSELVLVDNVFTYT  50
Spy57     1 MIITKKSLFVTSVALSLVPLATAQAQEWTPRSVTEIKSELVLVDNVFTYT  50
U09352    1 MIITKKSLFVTSVALSLAPLATAQAQEWTPRSVTEIKSELVLVDNVFTYT  50
Oklahoma  1 MIITKKSLFVTSVALSLVPLATAQAQEWTPRSVTEIKSELVLVDNVFTYT  50
          *****

12384      51 VKYGDTLSTIAEAMGIDVHVLGDNHIANIDLIFPDTILTANYNQHGQAT 100
2699      51 VKYGDTLSTIAEAMGIDVHVLGDNHIANIDLIFPDTILTANYNQHGQAT 100
B514      51 VKYGDTLSTIAEAMGIDVHVLGDNHIANIDLIFPDTILTANYNQHGQAT 100
Spy57     51 VKYGDTLSTIAEAMGIDVHVLGDNHIANIDLIFPDTILTANYNQHGQAT 100
U09352    51 VKYGDTLSTIAEAMGIDVHVLGDNHIANIDLIFPDTILTANYNQHGQAT 100
Oklahoma  51 VKYGDTLSTIAEAMGIDVHVLGDNHIANIDLIFPDTILTANYNQHGQAT 100
          *****

12384      101 TLTVQAPASSPASVSHVPSSEPLPQASATSQSTVPMAPSATPSDVPTTF 150
2699      101 TLTVQAPASSPASVSHVPSSEPLPQASATSQSTVPMAPSATPSDVPTTF 150
B514      101 TLTVQAPASSPASVSHVPSSEPLPQASATSQSTVPMAPSATP-----L 143
Spy57     101 NLTVQAPASSPASVSHVPSSEPLPQASATSQSTVPMAPPATPSDVPTTF 150
U09352    101 TLTVQAPASSPASVSHVPSSEPLPQASATSQSTIPMAPSATPSDVPTTPL 150
Oklahoma  101 NLTVQAPASSPASVSHVPSSEPLPQASATSQSTVPMAPPATPSDVPTTF 150
          *****

12384      151 ASAKPDSSVTASSELTSSTNDVSTELSSSESQKQPEVPQEA VPTPKAAETT 200
2699      151 ASAKPDSSVTASSELTSSTNDVSTELSSSESQKQPEVPQEA VPTPKAAEPT 200
B514      144 ASAKPDSSVTASSELTSSTNDVSTESSSESQKQPEVPQEA VPTPKAAETT 193
Spy57     151 ASAKPDSSVTASSELTSSTNDVSTELSSSESQKQPEVPQEA VPTPKAAETT 200
U09352    151 ASAKPDSFVTASSELTSSTNDVSTELSSSESQKQPEVPQEA EPTPKAAEST 200
Oklahoma  151 ASAKPDSSVTASSELTSSTNDVSTELSSSESQKQPEVPQEA VPTPKAAETT 200
          *****

12384      201 EVEPKTDISEDSTSANRPVPNESASEEVSSAAPAQAPAEKE---ETSAP 246
2699      201 EVEPKTDISEDPTSANRPVPNESASEEASSAAPAQAPAEKEETSQMLTAP 250
B514      194 EVEPKTDISEDPTSANRPVPNESASEEVSSAAPAQAPAEKE---ETSAP 239
Spy57     201 EVEPKTDISEAPTSANRPVPNESASEEVSSAAPAQAPAEKE---ETSAP 246
U09352    201 EVEPKTDISEDSTSANRPVPNGSASEEASSAAPAQAPAEKEETSQMLTAP 250
Oklahoma  201 EVEPKTDISEAPTSANRPVPNESASEEVSSAAPAQAPAEKE---ETSAP 246
          *****

12384      247 AAQKAVADTTSVATSNGLSYAPNHAYNPMNAGLQPQTAAFKEEVASAFGI 296
2699      251 AAQKAVADTTSVATSNGLSYAPNHAYNPMNAGLQPQTAAFKEEVASAFGI 300
B514      240 AAQKAVADTTSVATSNGLSYAPNHAYNPMNAGLQPQTAAFKEEVASAFGI 289
Spy57     247 AAQKAVADTTSVATSNGLSYAPNHAYNPMNAGLQPQTAAFKEEVASAFGI 296
U09352    251 AAQKAVADTTSVATSNGLSYAPNHAYNPMNAGLQPQTAAFKEEVLLPLVL 300
Oklahoma  247 AAQKAVADTTSVATSNGLSYAPNHAYNPMNAGLQPQTAAFKEEVASAFGI 296
          *****

12384      297 TSFSGYRPGDPGDHGKGLAIDFMPENSALGDQVAQY AIDHMAERGISYV 346
2699      301 TSFSGYRPGDPGDHGKGLAIDFMPVSSTLGDQVAQY AIDHMAERGISYV 350
B514      290 TSFSGYRPGDPGDHGKGLAIDFMPENSALGDQVAQY AIDHMAERGISYV 339
Spy57     297 TSFSGYRPGDPGDHGKGLAIDFMPENSALGDQVAQY AIDHMAERGISYV 346
U09352    301 RHLVVTVQEIQEIIGKGLAIDFMPVSSTLGDQVAQY AIDHMADGGISYV 350
Oklahoma  297 TSFSGYRPGDPGDHGKGLAIDFMPENSALGDQVAQY AIDHMAERGISYV 346
          *****

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12384	347	IWKQRFYAPFASIYGPAYTWNPMMPDRGSITENHYDHSVHVSFNA	389
2699	351	IWKQRFYAPFASIYGPAYTWNPMMPDRGSITENHYDHSVHVSFNA	393
B514	340	IWKQRFYAPFASIYGPAYTWNPMMPDRGSITENHYDHSVHVSFNA	382
Spy57	347	IWKQRFYAPFASIYGPAYTWNPMMPDRGSITENHYDHSVHVSFNA	389
U09352	351	IWKQRFYAPFASIYGPAYTWNPMMPDRGSITVPHYDHSVHVSFNA	393
Oklahoma	347	IWKQRFYAPFASIYGPAYTWNPMMPDRGSITENHYDHSVHVSFNA	389
*****			

Figure 19

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1  ATGAAGAAAA GAATGTTATT AGCGTCAACA GTAGCCTTGT CATTTGCCCC
51  AGTATTGGCA ACTCAAGCAG AAGAAGTTCT TTGGACTGCA CGTAGTGTTG
101 AGCAAATCCA AAACGATTTG ACTAAAACGG ACAACAAAAC AAGTTATACC
151 GTACAGTATG GTGATACTTT GAGCACCATT GCAGAAGCCT TGGGTGTAGA
201 TGTCACAGTG CTTGCGAATC TGAACAAAAT CACTAATATG GACTTGATTT
251 TCCCAGAAAC TGTTTGTACA ACGACTGTCA ATGAAGCAGA AGAAGTAACA
301 GAAGTTGAAA TCCAAACACC TCAAGCAGAC TCTAGTGAAG AAGTGACAAC
351 TGCAGACAGCA GATTTGACCA CTAATCAAGT GACCGTTGAT GATCAAACCTG
401 TTCAGGTTGC AGACCTTCTT CAACCAATTG CAGAAGTTAC AAAGACAGTG
451 ATTGCTTCTG AAGAAGTGGC ACCATCTACG GGCATTCTG TCCCAGAGGA
501 GCAAACGACC GAAACAACCTC GCCCAGTTGA AGAAGCAACT CCTCAGGAAA
551 CGACTCCAGC TGAGAAGCAG GAAACACAAG CAAGCCCTCA AGCTGCATCA
601 GCAGTGGGAG TAACTACAAC AAGTTCAGAA GCAAAGAAG TAGCATCATC
651 AAATGGAGCT ACAGCAGCAG TTTCTACTTA TCAACCAGAA GAGACGAAAA
701 TAATTTCAAC AACTTACGAG GCTCCAGCTG CGCCCGATTA TGCTGGACTT
751 GCAGTAGCAA AATCTGAAAA TGCAGGTCTT CAACCACAAA CAGCTGCCTT
801 TAAAGAAGAA ATTGCTAACT TGTTTGGCAT TACATCCTTT AGTGTTTATC
851 GTCCAGGAGA CAGTGGAGAT CACGGAAAAG GTTTGGCTAT CGACTTTATG
901 GTACCAGAAC GTTCAGAATT AGGGGATAAG ATTGCGGAAT ATGCTATTCA
951 AAATATGGCC AGCCGTGGCA TTAGTTACAT CATCTGGAAG CAACGTTTCT
1001 ATGCTCCATT CGATAGCAAA TATGGGCCAG CTAACACTTG GAACCCAATG
1051 CCAGACCGTG GTAGTGTGAC AGAAAATCAC TATGATCACG TTCACGTTTC
1101 AATGAATGGA TAA (SEQ ID NO:17)

```

Figure 20

```

1  MKKRMLLAST VALSFAPVLA TQAEVLWTA RSVEQIQNDL TKTDNKTSYT
51  VQYGDTLSTI AEALGVDVTV LANLNKITNM DLIFPETVLT TTVNEAEEVT
101 EVEIQTPQAD SSEEVTATA DLTTNQVTV DQTVQVADLS QPIAEVTKTV
151 IASEEVAPST GTSVPVEEQT ETTRPVEEAT PQETTPAEKQ ETQASPOAAS
201 AVEVTTTSSE AKEVASSNGA TAAVSTYQPE ETKIISTTYE APAAPDYAGL
251 AVAKSENAGL QPQTAAFKEE IANLFGITSF SGYRPGDSGD HGKGLAIDFM
301 VPERSELGDK IAEYAIQNMA SRGISYIIWK QRFYAPFDSK YGPANTWNPM
351 PDRGSVTENH YDHVHVSMNG * (SEQ ID NO:18)

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